```
=> file casreact
FILE 'CASREACT' ENTERED AT 15:52:04 ON 01 JUL 2004
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FILE CONTENT:1840 - 27 Jun 2004 VOL 140 ISS 26

************************************************************
*                                                          *
*     CASREACT now has more than  8 million reactions      *
*                                                          *
************************************************************

Some records from 1974 to 1991 are derived from the ZIC/VINITI data file
and provided by InfoChem and some records are produced using some INPI
data from the period prior to 1986.  Biotransformations database from
(1971-1998).

This file contains CAS Registry Numbers for easy and accurate substance
identification.

=> d que
L1              STR
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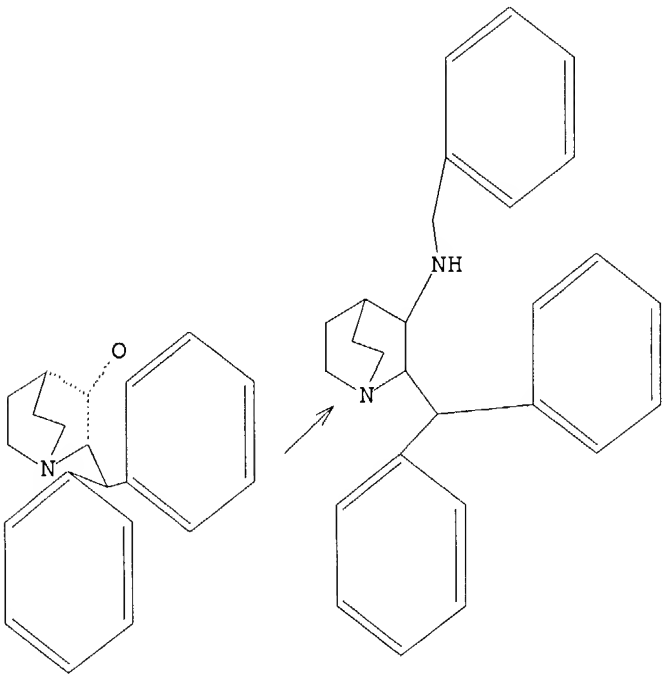


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Structure attributes must be viewed using STN Express query preparation.
L3            2 SEA FILE=CASREACT SSS FUL L1 (     7 REACTIONS)


=> d l3 1-2 ibib abs fcrd
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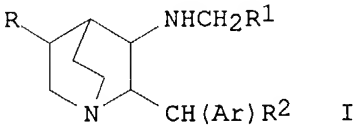
L3 ANSWER 1 OF 2 CASREACT COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 125:49301 CASREACT
TITLE: Preparation of quinuclidine derivatives as substance P antagonists
INVENTOR(S): Lowe, John Adams
PATENT ASSIGNEE(S): Pfizer Inc., India
SOURCE: Indian, 69 pp.
CODEN: INXXAP
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN 173570	A	19940604	IN 1989-DE1094	19891123

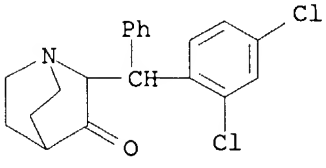
PRIORITY APPLN. INFO.: IN 1989-DE1094 19891123
OTHER SOURCE(S): MARPAT 125:49301
GI



I

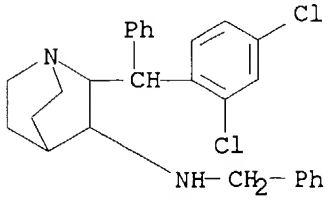
AB Quinuclidine derivs. [I; Ar = thienyl, Ph, halophenyl; R = H, C1-4 alkyl; R1 = C5-7 cycloalkyl, norbornyl, pyrrolyl, 2,3-dihydrobenzofuranyl, (alkoxy)thienyl, (hydroxy)pyridyl, quinolinyl, indolyl, (alkoxy)naphthyl, biphenyl, 2,3-methylenedioxyphenyl, substituted Ph, etc.; R2 = branched alkyl or alkenyl, C5-7 cycloalkyl, furyl, thienyl, (substituted) Ph, phenylalkyl, C1-3 alkoxy, etc.] are prepd. for use as substance P antagonists for treatment of gastrointestinal and central nervous (psychotic) disorders, inflammatory diseases, pain, and migraine. I are prepd. by redn. of the corresponding quinuclidine imine or amide. Thus, 3-keto-2-benzhydrylquinuclidine condensed with cyclohexylmethylamine to form an imine, which was reduced with 9-borabicyclononane in THF to cis-3-(cyclohexylmethylamino)-2-benzhydrylquinuclidine.

RX(4) OF 42



(step 1)

1. PhCH2NH2, 10-CSA, PhMe
2. 9-BBN, THF
3. Water



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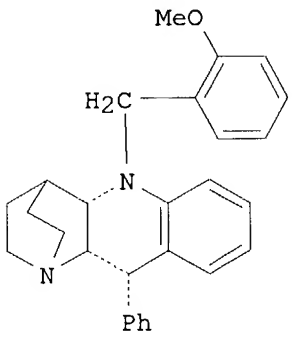
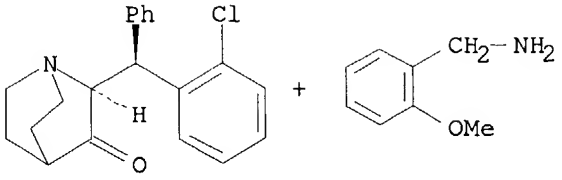
L3 ANSWER 2 OF 2 CASREACT COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 122:9904 CASREACT
TITLE: Synthesis of a benzo[b]-1,5-naphthyridine derivative as a potential constrained NK1 receptor antagonist
AUTHOR(S): Viti, Giovanni; Giannotti, Danilo; Nannicini, Rossano; Balacco, Giuseppe; Pestellini, Vittorio
CORPORATE SOURCE: Chem. Res. Dep., Firenze, 50131, Italy
SOURCE: Tetrahedron Letters (1994), 35(32), 5939-42
CODEN: TELEAY; ISSN: 0040-4039
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

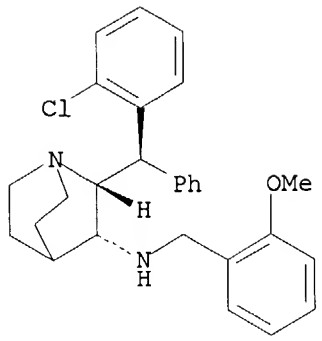


I

AB A short synthesis of a cyclic constrained analog I of the potent Substance P antagonist (.+-.)-CP-96345 is described. The key feature is the formation of the benzo[b]-1,5-naphthyridine system at the very last step of the synthesis through an intramol. arylation of an amine promoted by a strong base. If the tricyclic system was synthesized first, 2-methoxybenzylation of both the nitrogen atoms occurred.

RX(5) OF 9





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=> file casreact
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26, 1996), unless otherwise indicated in the original publications.

FILE CONTENT:1840 - 27 Jun 2004 VOL 140 ISS 26

************************************************************
*                                                          *
*     CASREACT now has more than  8 million reactions      *
*                                                          *
************************************************************

Some records from 1974 to 1991 are derived from the ZIC/VINITI data file
and provided by InfoChem and some records are produced using some INPI
data from the period prior to 1986.  Biotransformations database from
(1971-1998).

This file contains CAS Registry Numbers for easy and accurate substance
identification.

=> d que
L1              STR
```

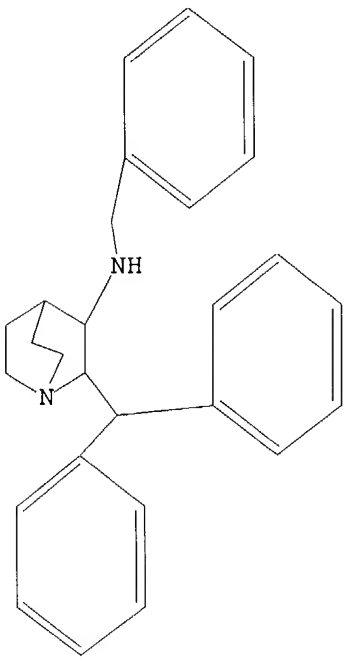


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Structure attributes must be viewed using STN Express query preparation.
L3            3 SEA FILE=CASREACT SSS FUL L1 (    32 REACTIONS)

=> d l3 1-3 ibib abs fcrd
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L3 ANSWER 1 OF 3 CASREACT COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 137:369932 CASREACT

TITLE: Cooperative problem solving: investigation into the oxidative degradation of CJ-11,974-01 and [14C]CJ-11,974-01

AUTHOR(S): Zandi, Kathleen S.; Huff, Barbara B.; Kamel, Amin; Larmann, John; Massefski, Walter W.; McCarthy, Keith E.; Miller, Sandra A.; Smith, Scott W.

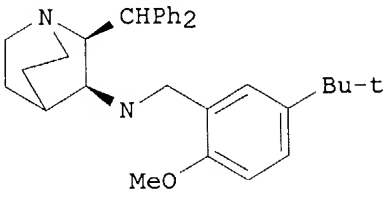
CORPORATE SOURCE: Radiochemical Synthesis Pfizer Central Research, Groton, CT, 06340, USA

SOURCE: Synthesis and Applications of Isotopically Labelled Compounds, Proceedings of the International Symposium, 7th, Dresden, Germany, June 18-22, 2000 (2001), Meeting Date 2000, 232-235. Editor(s): Pleiss, Ulrich; Voges, Rolf. John Wiley & Sons Ltd.: Chichester, UK.
CODEN: 69CIJC; ISBN: 0-471-49501-8

DOCUMENT TYPE: Conference

LANGUAGE: English

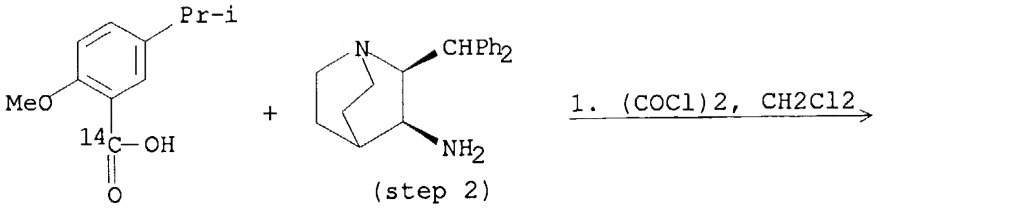
GI

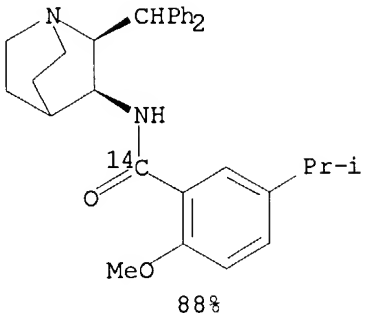


I

AB Bulk CJ-11,974-01 (I) is stable as a drug substance but degrades over time in some solid dosage formulations. Minor impurities were identified as synthetic intermediates and a major degradant has a mol. wt. of M+32 by mass spectral anal., suggesting the addn. of two oxygen atoms. Using soln. phase hydrogen/deuterium exchange and HPLC/ESI/MS/MS techniques, the degrdn. product was identified as the benzyl hydroperoxide deriv. The [14C]CJ-11,974-01 in ethanol soln. is quite stable but is unstable as a solid, degrading to the same M+32 degrdn. product over a relatively short period of time. Storage of solid [14C]CJ-11,974-01 under inert atm. or at lower temps. did not considerably slow the degrdn. The carbon-14 labeled degradant was isolated by normal and reverse phase chromatogs. and identified by NMR (NMR) spectroscopy and MS as the iso-Pr peroxide.

RX(2) OF 6





88%

NOTE: radiochem.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 3 CASREACT COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 125:49301 CASREACT
TITLE: Preparation of quinuclidine derivatives as substance P antagonists
INVENTOR(S): Lowe, John Adams
PATENT ASSIGNEE(S): Pfizer Inc., India
SOURCE: Indian, 69 pp.
CODEN: INXXAP
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN 173570	A	19940604	IN 1989-DE1094	19891123

PRIORITY APPLN. INFO.: IN 1989-DE1094 19891123
OTHER SOURCE(S): MARPAT 125:49301
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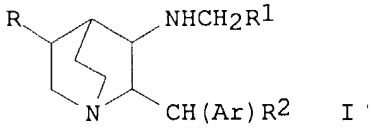
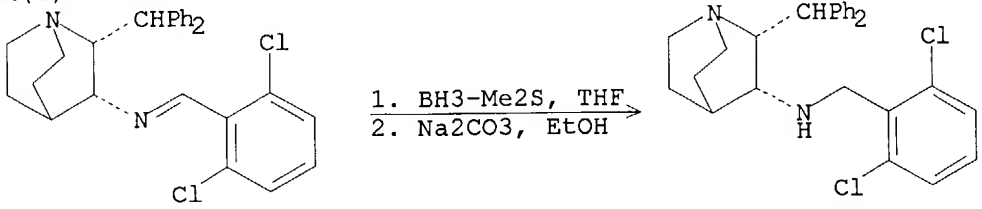


I

AB Quinuclidine derivs. [I; Ar = thienyl, Ph, halophenyl; R = H, C1-4 alkyl; R1 = C5-7 cycloalkyl, norbornyl, pyrrolyl, 2,3-dihydrobenzofuranyl,

(alkoxy)thienyl, (hydroxy)pyridyl, quinolinyl, indolyl, (alkoxy)naphthyl, biphenyl, 2,3-methylenedioxyphenyl, substituted Ph, etc.; R2 = branched alkyl or alkenyl, C5-7 cycloalkyl, furyl, thienyl, (substituted) Ph, phenylalkyl, C1-3 alkoxy, etc.] are prepd. for use as substance P antagonists for treatment of gastrointestinal and central nervous (psychotic) disorders, inflammatory diseases, pain, and migraine. I are prepd. by redn. of the corresponding quinuclidine imine or amide. Thus, 3-keto-2-benzhydrylquinuclidine condensed with cyclohexylmethylamine to form an imine, which was reduced with 9-borabicyclononane in THF to cis-3-(cyclohexylmethylamino)-2-benzhydrylquinuclidine.

RX(1) OF 42



(step 1) 31%

L3 ANSWER 3 OF 3 CASREACT COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 122:9904 CASREACT

TITLE: Synthesis of a benzo[b]-1,5-naphthyridine derivative as a potential constrained NK1 receptor antagonist

AUTHOR(S): Viti, Giovanni; Giannotti, Danilo; Nannicini, Rossano; Balacco, Giuseppe; Pestellini, Vittorio

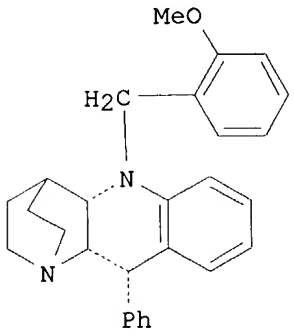
CORPORATE SOURCE: Chem. Res. Dep., Firenze, 50131, Italy

SOURCE: Tetrahedron Letters (1994), 35(32), 5939-42
CODEN: TELEAY; ISSN: 0040-4039

DOCUMENT TYPE: Journal

LANGUAGE: English

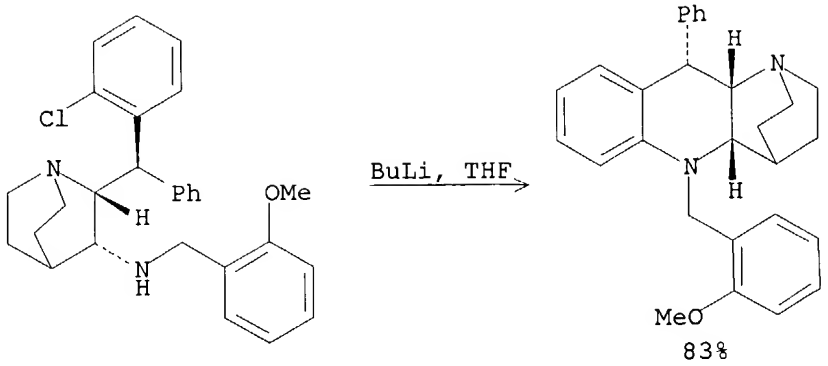
GI



I

AB A short synthesis of a cyclic constrained analog I of the potent Substance P antagonist (.+-.)-CP-96345 is described. The key feature is the formation of the benzo[b]-1,5-naphthyridine system at the very last step of the synthesis through an intramol. arylation of an amine promoted by a strong base. If the tricyclic system was synthesized first, 2-methoxybenzylation of both the nitrogen atoms occurred.

RX(1) OF 9



83%

=> file caplus
FILE 'CAPLUS' ENTERED AT 15:46:57 ON 01 JUL 2004
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FILE COVERS 1907 - 1 Jul 2004 VOL 141 ISS 1
FILE LAST UPDATED: 30 Jun 2004 (20040630/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d que
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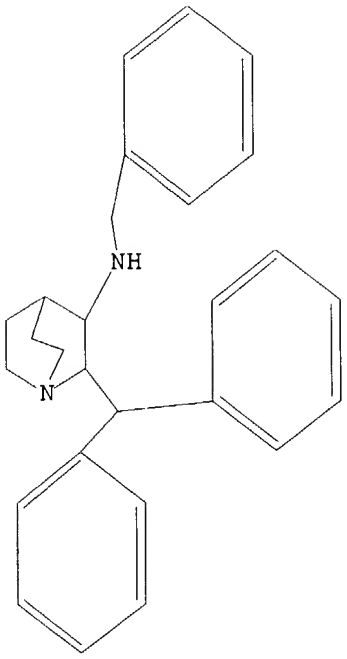

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L5 382 SEA FILE=REGISTRY SSS FUL L1
L7 46 SEA FILE=CAPLUS L5/P

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L7 ANSWER 1 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:354938 CAPLUS
DOCUMENT NUMBER: 140:375350
TITLE: Process for the preparation of (S,S)-cis-2-benzhydryl-3-benzylaminoquinuclidine from racemic 2-benzhydryl-3-quinuclidinone
INVENTOR(S): Nugent, Thomas C.; Seemayer, Robert
PATENT ASSIGNEE(S): Pfizer Prodoucts, Inc, USA; DSM Pharmaceuticals, Inc.
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004035575	A1	20040429	WO 2003-US32275	20031010

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,

NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004116704 A1 20040617 US 2003-679961 20031006

PRIORITY APPLN. INFO.: US 2002-419051P P 20021016

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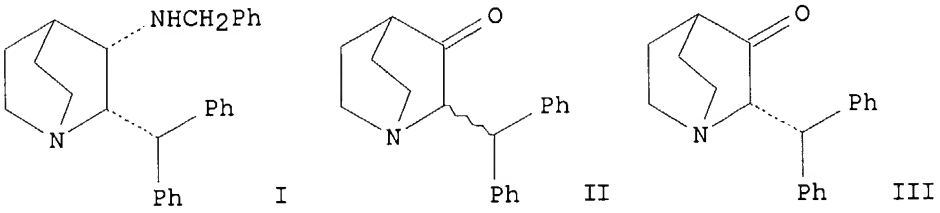


AB The present invention discloses a process for prepg. (S,S)-cis-2-benzhydryl-3-benzylaminoquinuclidine (I) from racemic 2-benzhydryl-3-quinuclidinone (II). The process includes the steps of contacting II with an effective amt. of a chiral org. acid in the presence of an org. solvent and an effective amt. of an org. carboxylic acid for converting the R-isomer into an acid salt of the S isomer, wherein the org. solvent is capable of solubilizing the compd. contg. the mixt. of R- and S-isomers, while pptg. the acid salt and the org. carboxylic acid is different from the chiral org. acid; neutralizing the acid salt with a base to provide an S-isomer of a chiral ketone III, and reacting III with an org. amine in the presence of a Lewis acid to provide the corresponding imine which was reduced to afford I .

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT **155681-48-4P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of (S,S)-cis-2-benzhydryl-3-benzylaminoquinuclidine from racemic 2-benzhydryl-3-quinuclidinone)

L7 ANSWER 2 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:886248 CAPLUS

DOCUMENT NUMBER: 141:6864

TITLE: Tritiation of nonpeptide substance P antagonist CP-96,345 and its azido analogue. Synthetic and characterization details

AUTHOR(S): Egan, Judith A.; Filer, Crist N.

CORPORATE SOURCE: PerkinElmer Life and Analytical Sciences, Inc., Boston, MA, 02118, USA

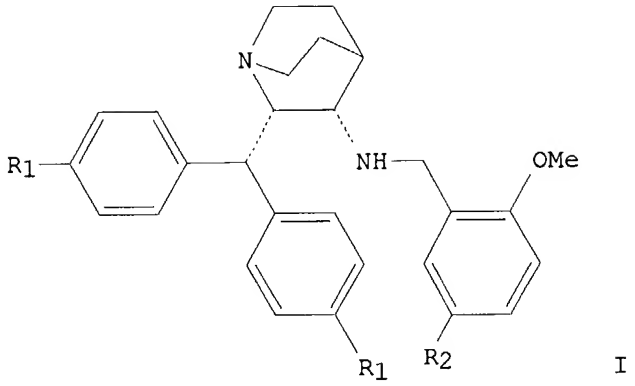
SOURCE: Applied Radiation and Isotopes (2003), 59(5-6), 333-335
CODEN: ARISEF; ISSN: 0969-8043

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



I

AB CP-96,345 was the first nonpeptide antagonist discovered for the SP receptor and [3H] CP-96,345 was required to study the mechanism of receptor action. The radioligand I (R1 = T, R2 = H) was prepd. at high specific activity by catalytic dehalogenation of a dibrominated precursor I (R1 = Br, R2 = H). The photoaffinity analog I (R1 = T, R2 = N3) was also prepd. from precursor I (R1 = Br, R2 = NH2) using the same approach followed by diazotization and azidation with NaN3.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT **695185-71-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of tritium labeled substance P antagonist CP-96,345 and its azido analog. via tritiation of suitable dibrominated precursor with tritium)

IT **135007-77-1P 695185-72-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of tritium labeled substance P antagonist CP-96,345 and its azido analog. via tritiation of suitable dibrominated precursor with tritium)

L7 ANSWER 3 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:174780 CAPLUS
DOCUMENT NUMBER: 137:369932
TITLE: Cooperative problem solving: investigation into the oxidative degradation of CJ-11,974-01 and [14C]CJ-11,974-01
AUTHOR(S): Zandi, Kathleen S.; Huff, Barbara B.; Kamel, Amin; Larmann, John; Massefski, Walter W.; McCarthy, Keith E.; Miller, Sandra A.; Smith, Scott W.
CORPORATE SOURCE: Radiochemical Synthesis Pfizer Central Research, Groton, CT, 06340, USA
SOURCE: Synthesis and Applications of Isotopically Labelled Compounds, Proceedings of the International Symposium, 7th, Dresden, Germany, June 18-22, 2000 (2001), Meeting Date 2000, 232-235. Editor(s): Pleiss, Ulrich; Voges, Rolf. John Wiley & Sons Ltd.: Chichester, UK.
CODEN: 69CIJC; ISBN: 0-471-49501-8
DOCUMENT TYPE: Conference
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:369932
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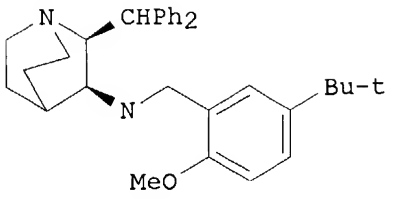


I

AB Bulk CJ-11,974-01 (I) is stable as a drug substance but degrades over time in some solid dosage formulations. Minor impurities were identified as synthetic intermediates and a major degradant has a mol. wt. of M+32 by mass spectral anal., suggesting the addn. of two oxygen atoms. Using soln. phase hydrogen/deuterium exchange and HPLC/ESI/MS/MS techniques, the degrdn. product was identified as the benzyl hydroperoxide deriv. The [14C]CJ-11,974-01 in ethanol soln. is quite stable but is unstable as a solid, degrading to the same M+32 degrdn. product over a relatively short period of time. Storage of solid [14C]CJ-11,974-01 under inert atm. or at lower temps. did not considerably slow the degrdn. The carbon-14 labeled degradant was isolated by normal and reverse phase chromatogs. and identified by NMR (NMR) spectroscopy and MS as the iso-Pr peroxide.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT 475146-68-0P **475146-69-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of carbon-14 labeled N-[[(dimethylethyl)methyoxyphenyl]methyl](diphenylmethyl)azabicyclo[2.2.2]octanamine [CJ-11,974-01] and identification of oxidative degrdn. product)

IT **475146-70-4P 475146-71-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of carbon-14 labeled N-[[(dimethylethyl)methyoxyphenyl]methyl](diphenylmethyl)azabicyclo[2.2.2]octanamine [CJ-11,974-01] and identification of oxidative degrdn. product)

L7 ANSWER 4 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:47520 CAPLUS
DOCUMENT NUMBER: 136:102294
TITLE: Preparation of fluoroalkoxybenzylamino derivatives of nitrogen containing heterocycles as substance P receptor antagonists
INVENTOR(S): Chappel, Phillip Branch; O'neill, Brian Thomas; Saltarelli, Mario David
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: Eur. Pat. Appl., 44 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1172106	A2	20020116	EP 2001-303983	20010501
EP 1172106	A3	20020515		

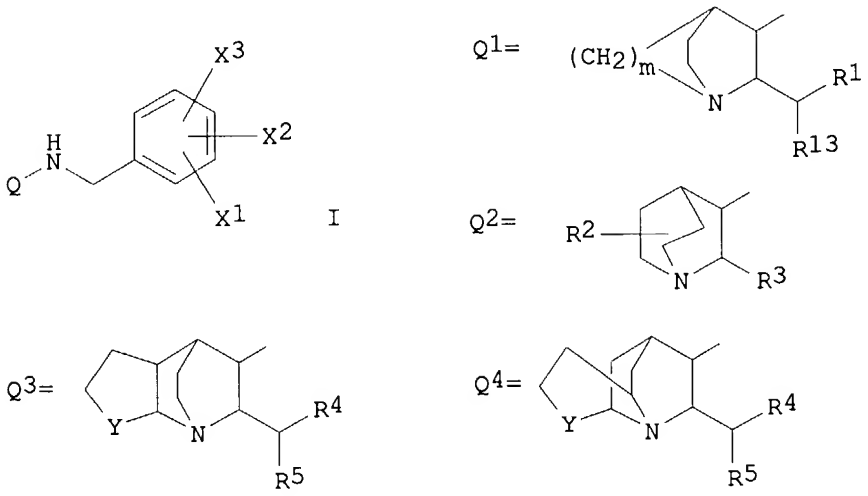
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

ZA 2001003484	A	20021202	ZA 2001-3484		20010430
CA 2345760	AA	20011103	CA 2001-2345760		20010501
JP 2002020287	A2	20020123	JP 2001-134144		20010501
US 2002035147	A1	20020321	US 2001-848069		20010503
US 2003114439	A1	20030619	US 2002-208274		20020729

PRIORITY APPLN. INFO.:
US 2000-201591P P 20000503
US 2000-237780P P 20001004
US 2001-848069 B1 20010503

OTHER SOURCE(S): MARPAT 136:102294

GI



AB The present invention relates to methods of treating various central nervous system (CNS) and other disorders or conditions by administering fluoroalkoxybenzylamino derivs. of nitrogen contg. heterocyclic compds., and specifically, by administering compds. of the formula [I; X1 = H, C1-10 alkoxy or alkyl optionally substituted with from one to three fluorine atoms; X2, X3 = halo, H, NO2, C1-10 alkyl or alkoxy optionally substituted with from one to three fluorine atoms, CF3, hydroxy, Ph, cyano, amino, C1-6 alkylamino, di(C1-6 alkyl)amino, -CONH-C1-6alkyl, C1-6 alkyl-CONH-C1-6 alkyl, hydroxy-C1-4 alkyl, C1-4 alkoxy-C1-4 alkyl, NHCHO, NHCO-C1-C6 alkyl; Q = N-contg. heterocyclyl, e.g. Q1, Q2, Q3, Q4; R1= furyl, thienyl, pyridyl, indolyl, biphenyl, (un)substituted phenyl; R13 = C3-4 branched alkyl, C5-6 branched alkenyl, C5-7 cycloalkyl, groups defined in R1; R2 = H, C1-6 alkyl; R3 = each (un)substituted Ph, biphenyl, naphthyl, pyridyl, benzhydryl, thienyl, or furyl; Y = (CH2)1 (wherein 1 = an integer from 1 to 3), or cyclohexane-1,2-diyl; Z = O, S, NH, C1-C3 alkyl-NH, (CH2)n (wherein n =0, 1,2); m = 2,3; R4 = furyl, thienyl, pyridyl, indolyl, biphenyl, (un)substituted phenyl; R5 = thienyl, biphenyl, (un)substituted phenyl] in a mammal. These compds. I are substance P receptor antagonists (no data). The above CNS and other disorders or conditions include sleep disorders, autism, pervasive development disorder, rheumatoid arthritis, osteoarthritis, fibromyalgia, human immunodeficiency virus (HIV) infections, dissociative disorders such as body dysmorphic disorders, eating disorder such as anorexia and bulimia, ulcerative colitis, Crohn's disease, irritable bowel syndrome, functional abdominal pain, chronic fatigue syndrome, sudden infant death syndrome (SIDS), overactive bladder, chronic cystitis, chemotherapy induced cystitis, cough, angiotensin converting enzyme (ACE) induced cough, itch, hiccups, premenstrual syndrome, premenstrual dysphoric disorder, schizophrenia, schizoaffective disorder, delusional disorder,

substance-induced psychotic disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition, schizophreniform disorder, and amenorrheic disorders such as dysmenorrhea. They also include obesity, epilepsy, movement disorders such as primary movement disorders, spasticities, Scott's syndrome, Tourette's syndrome, palsys, amyolateral sclerosis (ALS), akinetic-rigid disorders, akinesias, dyskinesias, restless leg syndrome and movement disorders assocd. with Parkinson's disease or Huntington's disease, mastalgia syndromes, motion sickness, immune dysfunctions, generalized anxiety disorder, panic disorder, phobias including social phobia, agoraphobia, and specific phobias, obsessive-compulsive disorder, posttraumatic stress disorder; depression including major depression, single episode depression, recurrent depression, child abuse induced depression, postpartum depression and dysthymia, cyclothymia, bipolar disorder, neurocardiac disorders such as neurocardiac syncope, neurogenic syncope, hypersensitive Carotid sinus, neurovascular syndrome and arrhythmias including arrhythmias secondary to gastrointestinal disturbances, addiction disorders involving addictions to behaviors, HIV-1 assocd. dementia, AIDS dementia complex, HIV encephalopathy, HIV related neuralgias, AIDS related neuralgias, epilepsy, and attention deficit hyperactivity disorder in a mammal. Thus, reductive alkylation of 2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine by 2-(difluoromethoxy)benzaldehyde using sodium cyanoborohydride in MeOH at room temp. for 30 h gave 2-(Diphenylmethyl)-N-[(2-difluoromethoxy)phenyl]methyl-1-azabicyclo[2.2.2]octan-3-amine.

IT **147249-22-7P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(Prepn. of fluoroalkoxybenzylamino derivs. of nitrogen contg. heterocycles as substance P receptor antagonists)

IT 145741-98-6P 145741-99-7P 145742-00-3P 145742-01-4P 145742-21-8P
145742-22-9P 145742-23-0P 145742-29-6P 145742-33-2P
147116-64-1P 147116-65-2P 147116-66-3P
147116-67-4P 147249-24-9P 155018-94-3P 157811-47-7P
157811-48-8P 190839-44-2P 209665-98-5P 209665-99-6P
209666-01-3P 209666-02-4P 209666-03-5P 209666-04-6P 209666-05-7P
209666-06-8P 209666-07-9P 209666-08-0P 209666-09-1P 209666-10-4P
209666-11-5P 209666-12-6P 209666-13-7P 209666-14-8P 209666-15-9P
209666-16-0P 209666-17-1P 209666-18-2P 209666-19-3P 209666-20-6P
209666-21-7P 209666-22-8P 209666-23-9P **209683-31-8P**
225526-07-8P 225526-17-0P 225526-19-2P 225526-22-7P 225526-24-9P
225655-10-7P 389091-60-5P 389091-63-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of fluoroalkoxybenzylamino derivs. of nitrogen contg. heterocycles as substance P receptor antagonists as therapeutic agents)

L7 ANSWER 5 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:896855 CAPLUS
DOCUMENT NUMBER: 136:193613
TITLE: Mechanism of cytochrome P4503A4- and 2D6-catalyzed dehydrogenation of ezlopitant as probed with isotope effects using five deuterated analogs
AUTHOR(S): Obach, R. Scott
CORPORATE SOURCE: Department of Drug Metabolism, Pfizer Global Research and Development, Groton, CT, 06340, USA
SOURCE: Drug Metabolism and Disposition (2001), 29(12), 1599-1607
CODEN: DMDSAI; ISSN: 0090-9556

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Ezlopitant is metabolized by cytochrome P 450 primarily to two metabolites: a benzyl alc. and a corresponding alkene. The alkene arises as a direct product of metab. of ezlopitant rather than through dehydration of the benzyl alc. The mechanism of this cytochrome P 450 (P 450)-catalyzed dehydrogenation reaction was probed with five different deuterium-labeled analogs of ezlopitant. At satg. ezlopitant concns., deuterium substitution resulted in small differences in reaction velocity. When deuterium was incorporated into the benzylic position ([d1]ezlopitant and [d7]ezlopitant), low isotope effects on the formation of both the benzyl alc. and alkene were obsd. (1.25-1.55 for CYP3A4 and 1.48-2.61 for CYP2D6), suggesting that abstraction of the benzylic hydrogen is obligatory in the formation of both metabolites. A small amt. of metabolic switching occurred because isotope effects were slightly higher for alkene and alc. formation than for ezlopitant consumption. Intramol. deuterium isotope effects of the dehydrogenation reaction for tri- and tetradeuterated analogs were very low (1.13-1.15) for both CYP3A4 and CYP2D6, whereas intramol. isotope effects for the chem. dehydration of correspondingly deuterated ezlopitant benzyl alc. (CJ-12,764) were 3.8 to 5.9. Thus, dehydrogenation does not appear to occur via enzyme-mediated general acid catalysis of the benzyl alc. A mechanism for the dehydrogenation of ezlopitant is proposed in consideration of the data presented.
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
IT **156749-85-8P**, CJ 12458 **161011-07-0P**, CJ 12764
400865-64-7P 400865-66-9P 400865-67-0P
400865-68-1P 400865-69-2P 400865-70-5P
400865-71-6P 400865-72-7P 400865-73-8P
400865-74-9P
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(mechanism of cytochrome P 4503A4- and 2D6-catalyzed dehydrogenation of ezlopitant as probed with isotope effects)

L7 ANSWER 6 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:704687 CAPLUS
DOCUMENT NUMBER: 135:262237
TITLE: Ferrous compounds as antioxidants for pharmaceutical formulations
INVENTOR(S): Wang, Hai
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: Jpn. Kokai Tokkyo Koho, 6 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2001261577	A2	20010926	JP 2001-68073	20010312
EP 1145719	A2	20011017	EP 2001-302022	20010306
EP 1145719	A3	20011114		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
CA 2339705	AA	20010910	CA 2001-2339705	20010308
BR 2001000949	A	20011030	BR 2001-949	20010309

US 2001047034	A1	20011129	US 2001-803455	20010309
US 6423351	B2	20020723		
US 2002183392	A1	20021205	US 2002-155157	20020524

PRIORITY APPLN. INFO.: US 2000-188447P P 20000310
US 2001-803455 A3 20010309

AB This invention relates to the use of Fe(II) compds. to prevent oxidn. degrdn. of easily oxidizable active ingredients in the compns. The easily oxidizable compds. contain .gtoreq. 1 benzyl or amine functional groups. (2S,3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine was mixed with ferrous ammonium sulfate hexahydrate (0.01 %)-contg. Avicel, then blended with Mg stearate for tableting. After storage of the tablets at 40.degree. and 75 % relative humidity for 6 wk, negligible amts. of oxidn. products were detected by reversed HPLC.

IT **161011-07-0P 362026-31-1P** 362026-33-3P
RL: BYP (Byproduct); PREP (Preparation)
(ferrous compds. as antioxidants for pharmaceutical formulations)

L7 ANSWER 7 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:911252 CAPLUS
DOCUMENT NUMBER: 134:42073
TITLE: Polymorphs of crystalline (2-benzhydryl-1-azabicyclo[2,2,2]oct-3-yl)-(5-isopropyl-2-methoxybenzyl)ammonium chloride as NK-1 receptor antagonists
INVENTOR(S): Allen, Douglas John Meldrum; Appleton, Troy Anthony; Gumkowski, Michael Jon; Muehlbauer, David Joseph; Norris, Timothy
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: PCT Int. Appl., 12 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000078759	A1	20001228	WO 2000-IB756	20000606
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6262067	B1	20010717	US 2000-564528	20000504
BR 2000011835	A	20020305	BR 2000-11835	20000606
EP 1187834	A1	20020320	EP 2000-929745	20000606
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, MC, PT, IE, SI, LT, LV, FI, RO				
TR 200103688	T2	20021223	TR 2001-20010368820000606	
EE 200100698	A	20030217	EE 2001-698	20000606
NZ 515348	A	20030725	NZ 2000-515348	20000606
AU 767336	B2	20031106	AU 2000-47745	20000606
AU 2000047745	A5	20010109		
BG 106205	A	20020731	BG 2001-106205	20011210
HR 2001000920	A1	20030228	HR 2001-920	20011211
NO 2001006187	A	20011218	NO 2001-6187	20011218

ZA 2001010387 A 20021219 ZA 2001-10387 20011219
PRIORITY APPLN. INFO.: US 1999-140233P P 19990622
WO 2000-IB756 W 20000606

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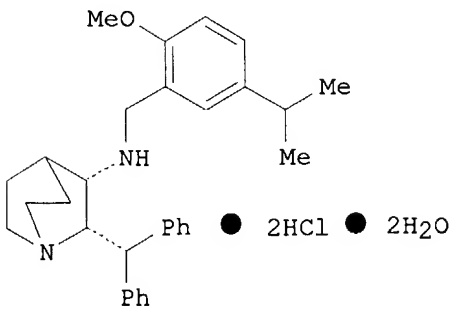


I

AB Two cryst. polymorphic forms of 2-(diphenylmethyl)-N-[[2-methoxy-5-(1-methylethyl)phenyl]methyl]-1-azabicyclo[2.2.2]octan-3-amine dihydrochloride dihydrate (I) were prepd. for use as NK-1 receptor antagonists. The pharmaceutical compn. contg. at least one of these polymorphs has advantageous stability for formulation to treat emesis in patients receiving chemotherapy. The administration of this pharmaceutical compn. is conventional oral by preferably tablet or capsule or i.v.

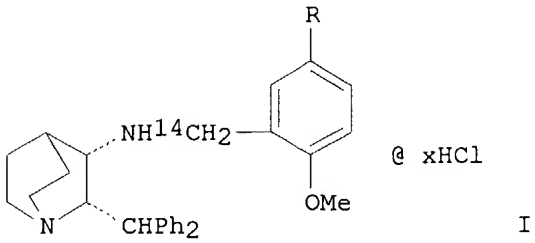
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT **312968-98-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of polymorphs of 2-(diphenylmethyl)-N-[[2-methoxy-5-(1-methylethyl)phenyl]methyl]-1-azabicyclo[2.2.2]octan-3-amine dihydrochloride cryst. as NK-1 receptor antagonists)

IT **223389-63-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of polymorphs of 2-(diphenylmethyl)-N-[[2-methoxy-5-(1-methylethyl)phenyl]methyl]-1-azabicyclo[2.2.2]octan-3-amine dihydrochloride cryst. as NK-1 receptor antagonists)

L7 ANSWER 8 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:902456 CAPLUS
DOCUMENT NUMBER: 134:266175
TITLE: Synthesis and stability of substance P antagonists [14C]CJ-11,974-01 and [14C]CJ-11,972-01
AUTHOR(S): Zandi, K. S.; Miller, S. A.; McCarthy, K. E.; Massefski, W. W.; Kamel, A.
CORPORATE SOURCE: Radiochemical Synthesis, Pfizer Central Research, Groton, CT, 06340, USA
SOURCE: Isotope Production and Applications in the 21st Century, Proceedings of the International Conference on Isotopes, 3rd, Vancouver, BC, Canada, Sept. 6-10, 1999 (2000), Meeting Date 1999, 400-402. Editor(s): Stevenson, Nigel R. World Scientific Publishing Co. Pte. Ltd.: Singapore, Singapore.

CODEN: 69ATWE
DOCUMENT TYPE: Conference
LANGUAGE: English
GI



I

AB CJ-11,974-01 (I, R = CHMe2) and CJ-11,972-01 (I, R = CMe3) are structurally related substance P antagonists currently in development (-01 indicates the HCl salt). The synthesis of radiolabeled analogs was completed to aid in full ADME characterization. A straightforward route to both compds. was developed via directed lithiation/metal halogen exchange and carbonation. Conversion to the benzylic amine was accomplished by one of two methods. In the case of [14C]CJ-11,974-01, the carboxylic acid chloride was treated with a chiral amine followed by amide redn., and for [14C]CJ-11,972-01, conversion to the aldehyde was followed by reductive amination. While both [14C]CJ-11,974-01 and [14C]CJ-11,972-01 are quite stable in soln., when stored as a solid, [14C]CJ-11,974-01 degrades to one major degrdn. product over a relatively short time period. The carbon-14 labeled degrdn. product was isolated from low specific activity material and identified by HPLC/MS/MS and NMR to be an iso-Pr peroxide. Studies were performed to identify the factors responsible for the oxidative degrdn. of [14C]CJ-11,974-01, which included salt form, storage conditions and salt formation solvent. Of all the variables studied over a three week period, only a change in the salt form prevented this oxidative degrdn.

IT **331676-67-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and degrdn. of)

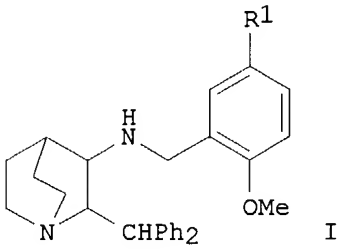
IT **331676-69-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

L7 ANSWER 9 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:518291 CAPLUS
DOCUMENT NUMBER: 131:157710
TITLE: Preparation of quinuclidine derivatives
INVENTOR(S): Ito, Fumitaka; Kondo, Hiroshi; Nakane, Masami; Shimada, Kaoru; Lowe, John Adams, III; Rosen, Terry Jay
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: U.S., 7 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

US 5939433	A	19990817	US 1997-846909	19970430

PRIORITY APPLN. INFO.: US 1997-846909 19970430
OTHER SOURCE(S): MARPAT 131:157710
GI



I

AB The title compds. I (R1 = Me, Et, iso-Pr, sec-Bu and tert-butyl) and its pharmaceutically acceptable salts were prepd. as substance P antagonists and useful in the treatment of gastrointestinal disorders, inflammatory disorders, central nervous system disorders and pain (no data). Thus, (2S,3S)-N-(2-methoxyphenylmethyl)-2-(diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-amine underwent hydrogenolysis followed by reductive condensation with 5-isopropyl-2-methoxybenzaldehyde in presence of triacetoxyborohydride to give (2S,3S)-N-(5-isopropyl-2-methoxyphenylmethyl)-2-(diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-amine methanesulfonate.

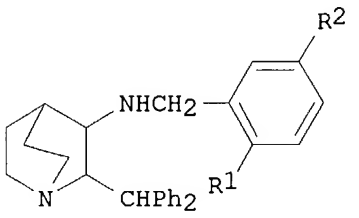
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT **147780-91-4P 147780-92-5P 147780-93-6P**
212957-56-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of pharmaceutically active quinuclidine derivs.)

L7 ANSWER 10 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:604662 CAPLUS
DOCUMENT NUMBER: 129:230640
TITLE: Preparation of 2-diphenylmethyl-3-(benzylamino)quinuclidine derivatives as substance P antagonists
INVENTOR(S): Ito, Fumitaka; Kondo, Hiroshi; Nakane, Masami; Shimada, Kaoru; Lowe, John Adams, III; Rosen, Terry Jay
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: U.S., 7 pp., Cont.-in-part of U.S. Ser. No. 708,404, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5807867	A	19980915	US 1994-211120	19940523

WO 9221677 A1 19921210 WO 1992-US3317 19920428
W: AU, BG, BR, CA, CS, DE, FI, HU, JP, KR, NO, PL, RO, RU, US
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GN, GR, IT, LU, MC, ML, MR, NL, SE, SN, TD, TG
US 6222038 B1 20010424 US 1995-377552 19950124
PRIORITY APPLN. INFO.: US 1991-708404 B2 19910531
WO 1992-US3317 W 19920428
US 1994-211120 A3 19940523
OTHER SOURCE(S): MARPAT 129:230640
GI



I

AB Compds. of the formula (I; wherein R1 is methoxy and R2 is selected from the group consisting of Me, Et, iso-Pr, sec-Bu and tert-butyl) and the pharmaceutically acceptable salts of such compds. are prepd. These compds. are substance P antagonists and useful in the treatment of gastrointestinal disorders, inflammatory disorders, central nervous system disorders and pain (no data). Thus, triacetoxy borohydride was added in portions to a soln. of 5-isopropoxy-2-methoxybenzaldehyde and (2S,3S)-N-(2-methoxyphenyl)methyl-1-azabicyclo[2.2.2]-octan-3-amine in CH2Cl2 and the resulting mixt. was stirred until the amine disappeared to give I (R1 = OMe, R2 = iso-Pr).
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
IT **147116-64-1P 147116-65-2P 147780-91-4P**
147780-92-5P 147780-93-6P 190839-44-2P
212957-56-7P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of diphenylmethyl(benzylamino)quinuclidine derivs. as substance P antagonists)

L7 ANSWER 11 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:430066 CAPLUS
DOCUMENT NUMBER: 129:95404
TITLE: Preparation of [(Fluoroalkoxy)benzylamino]piperidine derivatives as substance P receptor antagonists
INVENTOR(S): Lowe, John Adams, III; Rosen, Terry Jay
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: U.S., 19 pp., Cont.-in-part of U. S. 717,943, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5773450	A	19980630	US 1993-167881	19931214
WO 9300331	A1	19930107	WO 1992-US3571	19920505

W: AU, BR, CA, CS, DE, FI, HU, JP, KR, NO, PL, RU, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE

HU 70499	A2	19951030	HU 1995-836		19920505
US 5744480	A	19980428	US 1995-443418		19950522
US 2003199540	A1	20031023	US 2003-379198		20030304
PRIORITY APPLN. INFO.:			US 1991-717943	B2	19910620
			WO 1992-US3571	W	19920505
			US 1993-167881	A3	19931214
			HU 1993-3668	A	19931220
			US 1998-7268	A1	19980114

OTHER SOURCE(S): MARPAT 129:95404

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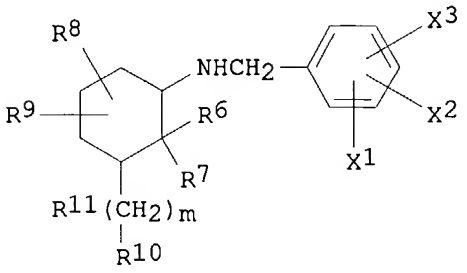

I

AB The present invention relates to novel fluoroalkoxybenzylamino derivs. of nitrogen contg. heterocyclic compds. [I; X1 = H, C1-10 alkoxy or C1-10 alkyl each optionally substituted with 1-3 F atoms; X2, X3 = halo, H, NO2, C1-10 alkoxy optionally substituted with 1-3 F atoms, C1-10 alkyl optionally substituted with 1-3 F atoms, CF3, OH, Ph, cyano, etc.; m = 0-8; any one of the carbon-carbon single bonds of (CH2)m may optionally be replaced by a CH:CH or C.tplbond.C and any of the carbon atoms of said (CH2)m may be optionally substituted with R11; R6 = H, straight or branched alkyl, C3-7 cycloalkyl (wherein one of the carbon atoms may be optionally replaced by N, O, or S), aryl, phenyl-C2-6 alkyl, etc.; R7 = h, Ph, C1-6 alkyl; or CR6R6 forms a C3-7 satd. carbocyclic ring wherein one of the ring carbon atoms may be replaced by O, N, or S; R8, R9 = H, OH, halo, NH2, oxo, cyano, hydroxy-C1-6 alkyl, C1-6 alkoxy-C1-6 alkyl, C1-6 alkylamino, di(C1-6 alkyl)amino, C1-6 alkoxy, C1-6 alkoxy-carbonyl, etc.; or R8 and R9 together with the carbon to which they are attached , form a C3-6 satd. carbocyclic ring that forms a spiro compd. with the N-contg. ring to which they are attached; R10 = acylamino, sulfonylamino, a radical listed in R6, R8, and R9; R11 = :NOH, OH, halo, NH2, etc.]. These novel compds. are useful in the treatment of inflammatory and central nervous system disorders, as well as other disorders (no data). The few antagonists thus far described in the recent past are generally peptide-like in nature and are therefore too labile from a metabolic point of view to serve as practical therapeutic agents in the treatment of disease. The non-peptidic antagonists of the present invention, on the other hand, do not possess this drawback, being far more stable from a metabolic point of view than the agents referred to above. Thus, (2S,3S)-3-amino-2-phenylpiperidine underwent reductive alkylation by 2-(2,2,2-trifluoroethoxy)benzaldehyde using sodium triacetoxyborohydride in AcOH to give (2S,3S)-2-phenyl-3-[2-(2,2,2-trifluoroethoxy)benzylamino]piperidine hydrochloride.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT 145741-98-6P 145741-99-7P 145742-00-3P 145742-01-4P 145742-28-5P
145742-29-6P 145742-33-2P **147249-22-7P** 155018-94-3P
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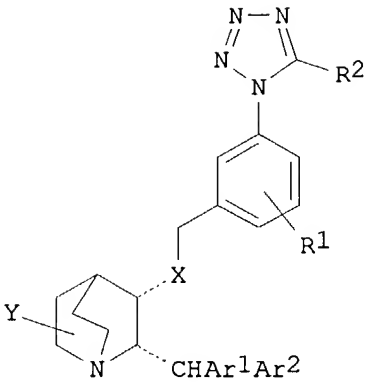
209666-18-2P 209666-19-3P 209666-20-6P 209666-21-7P 209666-22-8P
209666-23-9P **209683-31-8P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of [(Fluoroalkoxy)benzylamino]piperidine derivs. as substance P receptor antagonists as central nervous system agents and antiinflammatory agents)

L7 ANSWER 12 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:183916 CAPLUS
DOCUMENT NUMBER: 128:230552
TITLE: Preparation of tetrazolyl-substituted quinuclidines as substance P antagonists
INVENTOR(S): Satake, Kunio
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 829480	A2	19980318	EP 1997-306612	19970828
EP 829480	A3	19980408		
EP 829480	B1	20001220		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
AT 198201	E	20010115	AT 1997-306612	19970828
ES 2152633	T3	20010201	ES 1997-306612	19970828
PT 829480	T	20010430	PT 1997-306612	19970828
US 5939434	A	19990817	US 1997-924171	19970905
CA 2215020	AA	19980312	CA 1997-2215020	19970910
CA 2215020	C	20000516		
JP 10087661	A2	19980407	JP 1997-262965	19970911
JP 3273750	B2	20020415		
GR 3035379	T3	20010531	GR 2001-400206	20010207

PRIORITY APPLN. INFO.: WO 1996-IB934 W 19960912
EP 1997-306612 A 19970828
OTHER SOURCE(S): MARPAT 128:230552
GI



I

AB The title compds. I (R1 = halo, C1-C6-alkyl, halo-C1-C6-alkyl, C1-C6-alkoxy or halo-C1-C6-alkoxy; R2 = H, C1-C6-alkyl, halo-C1-C6-alkyl, C1-C6-alkylthio, C1-C6-alkylsulfinyl-, C1-C6-alkylsulfonyl, cyclopropyl, Ph, NH2, NHMe, -NHC(:O)Me, NMe2, NEt2 or -CH2C(:O)CF3; Ar1 and Ar2 are independently Ph, halophenyl or thienyl; X = NH, O or S; Y = H, -COOR3 or -CONR4R5, wherein R3, R4 and R5 are independently hydrogen or C1-C6 alkyl) and their pharmaceutically acceptable salts were prepd. These compds. are useful as analgesics or anti-inflammatory agents, or in the treatment of allergic disorders, angiogenesis, CNS disorders, emesis, gastrointestinal disorders, sunburn, urinary incontinence, or esp. as analgesics or anti-inflammatory agents in the periphery (no data). Thus, (2S,3S)-2-(diphenylmethyl)-1-azabicyclo[2.2.2]octane-3-amine was treated with 2-methoxy-5-(5-trifluoromethyltetrazol-1-yl)benzaldehyde in CH2Cl2 contg. sodium triacetoxyborohydride and AcOH to give (2S,3S)-3-[2-methoxy-5-(5-trifluoromethyltetrazol-1-yl)benzylamino]-2-(diphenylmethyl)-1-azabicyclo[2.2.2]octane.

IT **204688-23-3P 204688-24-4P 204688-25-5P**
204688-26-6P 204688-27-7P 204688-28-8P
204688-29-9P 204688-30-2P 204688-31-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of tetrazolyl-substituted quinuclidines as substance P antagonists)

L7 ANSWER 13 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:567054 CAPLUS
DOCUMENT NUMBER: 127:243327
TITLE: Characterization of non-peptide antagonist and peptide agonist binding sites of the NK1 receptor with fluorescent ligands
AUTHOR(S): Turcatti, Gerardo; Zoffmann, Sannah; Lowe, John A., III; Drozda, Susan E.; Chassaing, Gerard; Schwartz, Thue W.; Chollet, Andre
CORPORATE SOURCE: Geneva Biomedical Research Institute, Glaxo Wellcome, Geneva, CH-1228, Switz.
SOURCE: Journal of Biological Chemistry (1997), 272(34), 21167-21175
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Ligand recognition of the NK1 receptor (substance P receptor) by peptide

agonist and non-peptide antagonist has been investigated and compared by the use of fluorescent ligands and spectrofluorometric methods. Analogs of substance P (SP) labeled with the environment-sensitive fluorescent group 5-dimethylaminonaphthalene-1-sulfonyl (dansyl) at either position 3, 8, or 11 or with fluorescein at the N.alpha. position were synthesized and characterized. Peptides modified at the .alpha.-amino group or at positions 3 or 11 conserved a relatively good affinity for NK1 and agonistic properties. Modification at position 8 resulted in an 18,000-fold decrease in affinity. A fluorescent dansyl analog of the non-peptide antagonist CP 96,345 was prepd. and characterized. The quantum yield of fluorescence for dansyl-CP 96,345 was much higher than for any of the dansyl-labeled peptides indicating that the microenvironment of the binding site is more hydrophobic for the non-peptide antagonist than for the peptide agonists. Comparison of collisional quenching of fluorescence by the water-sol. hydroxy-Tempo compd. showed that dansyl-CP 96,345 is buried and virtually inaccessible to aq. quenchers, whereas dansyl- or fluoresceinyl-labeled peptides were exposed to the solvent. Anisotropy of all fluorescent ligands increased upon binding to NK1 indicating a restricted motional freedom. However, this increase in anisotropy was more pronounced for the dansyl attached to the non-peptide antagonist CP 96,345 than for the fluorescent probes attached to different positions of SP. In conclusion, our data indicate that the environment surrounding non-peptide antagonist and peptide agonists are vastly different when bound to the NK1 receptor. These results support recent observations by mutagenesis and crosslinking work suggesting that peptide agonists have their major interaction points in the N-terminal extension and the loops forming the extracellular face of the NK1 receptor. Our data also suggest that neither the C terminus nor the N terminus of SP appears to penetrate deeply below the extracellular surface in the transmembrane domain of the receptor.

IT **195886-19-2P**
RL: ARG (Analytical reagent use); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); USES (Uses)
(NK1 receptor nonpeptide antagonist and peptide agonist binding site characterization with fluorescent ligands)

IT **160502-78-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(fluorescent ligand prepn. for NK1 receptor)

L7 ANSWER 14 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:184712 CAPLUS
DOCUMENT NUMBER: 126:171491
TITLE: Resolution of N-[[2-methoxy-5-(1-methylethyl)phenyl]methyl]-2-(diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-amine with (1R)-(-)-10-camphorsulfonic acid
INVENTOR(S): Tickner, Derek L.; Meltz, Morgan
PATENT ASSIGNEE(S): Pfizer Inc., USA; Tickner, Derek L.; Meltz, Morgan
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9703984	A1	19970206	WO 1996-IB648	19960704
W: AU, CA, CN, CZ, HU, IL, JP, KR, MX, NO, NZ, PL, RU, SG, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				

CA 2227194	AA	19970206	CA 1996-2227194	19960704
CA 2227194	C	20020212		
AU 9661348	A1	19970218	AU 1996-61348	19960704
AU 697553	B2	19981008		
EP 840735	A1	19980513	EP 1996-918801	19960704
EP 840735	B1	20030924		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
CN 1190970	A	19980819	CN 1996-195567	19960704
CN 1068598	B	20010718		
RU 2136681	C1	19990910	RU 1998-101101	19960704
JP 3043074	B2	20000522	JP 1997-506471	19960704
JP 10511102	T2	19981027		
PL 184261	B1	20020930	PL 1996-324610	19960704
AT 250600	E	20031015	AT 1996-918801	19960704
PT 840735	T	20040227	PT 1996-918801	19960704
ES 2205039	T3	20040501	ES 1996-918801	19960704
ZA 9606026	A	19980116	ZA 1996-6026	19960716
US 6008357	A	19991228	US 1997-981750	19971216
NO 9800211	A	19980316	NO 1998-211	19980116
HK 1010195	A1	20011116	HK 1998-111206	19981013

PRIORITY APPLN. INFO.: US 1995-1191P P 19950717
WO 1996-IB648 W 19960704

AB The title amine (I) is resolved by treatment with (1R)-(-)-10-camphorsulfonic acid in a solvent which is selective for the salt of (2R,3R)-I, purifying the slurry of the (2S,3S)-I salts with the same solvent, and hydrolyzing the purified salt. Thus, (2S,3S)-I was obtained 99.5% pure when MeCN was used as the solvent.

IT **187281-31-8P**
RL: PUR (Purification or recovery); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(resoln. of [methoxyphenylmethyl](diphenylmethyl)azabicyclo[2.2.2]octan amine with camphorsulfonic acid)

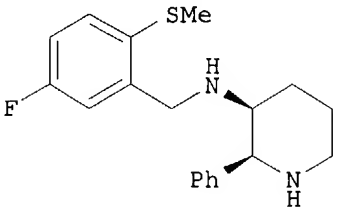
IT **147116-64-1P 187281-36-3P**
RL: PUR (Purification or recovery); SPN (Synthetic preparation); PREP (Preparation)
(resoln. of [methoxyphenylmethyl](diphenylmethyl)azabicyclo[2.2.2]octan amine with camphorsulfonic acid)

IT **187281-30-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(resoln. of [methoxyphenylmethyl](diphenylmethyl)azabicyclo[2.2.2]octan amine with camphorsulfonic acid)

L7 ANSWER 15 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:646442 CAPLUS
DOCUMENT NUMBER: 125:300828
TITLE: Nonaromatic heterocycles containing substituted benzylamine nitrogen, useful as substance P receptor antagonists.
INVENTOR(S): Howard, Harry R., Jr.; Ikunaka, Masaya; Ito, Fumitaka; Lowe, John A., III; Nakane, Masami; O'Neill, Brian T.
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: Span., 52 pp.
CODEN: SPXXAD
DOCUMENT TYPE: Patent
LANGUAGE: Spanish
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

ES 2087813 A1 19960716 ES 1993-1771 19930809
ES 2087813 B1 19970201
PRIORITY APPLN. INFO.: ES 1993-1771 19930809
OTHER SOURCE(S): MARPAT 125:300828
GI



II

AB Title compds. R1A(W)CH2NR2R3 (I) are claimed [wherein A = benzene, naphthalene, thiophene, dihydroquinoline, or indoline nucleus (amine-bearing sidechain is attached to a ring C atom); W = H, alkyl, alkylthio, halo, (fluoro)alkoxy; R1 = (un)substituted amino, alkyl- or arylthio, -sulfinyl, or -sulfonyl, aryloxy, etc.; R2 = H, alkoxycarbonyl; R3 = various N-contg. aliph. mono-, bi-, and polycyclic systems, attached at a C atom], as well as their pharmaceutically acceptable salts. I are substance P receptor antagonists (no data), useful as antiinflammatories, CNS agents, etc. Examples cover prepn. of approx. 60 invention compds., 50 intermediates, plus a variety of salts and/or free bases. For example, formylation of p-FC6H4SMe with MeOCHCl2 and TiCl4 gave 5-fluoro-2-(methylthio)benzaldehyde, which underwent reductive amination with cis-3-amino-6-oxo-2-phenylpiperidine and subsequent redn. of the oxo group with BH3.THF to give title compd. II.

IT 145741-93-1P 145741-94-2P 145741-95-3P 145741-96-4P 145877-16-3P
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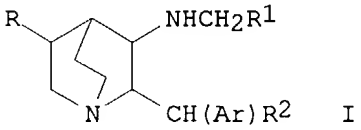
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of nonarom. heterocyclic benzylamine derivs. as substance P receptor antagonists)

L7 ANSWER 16 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:365745 CAPLUS
DOCUMENT NUMBER: 125:49301
TITLE: Preparation of quinuclidine derivatives as substance P antagonists
INVENTOR(S): Lowe, John Adams
PATENT ASSIGNEE(S): Pfizer Inc., India
SOURCE: Indian, 69 pp.
CODEN: INXXAP
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN 173570	A	19940604	IN 1989-DE1094	19891123

PRIORITY APPLN. INFO.: IN 1989-DE1094 19891123
OTHER SOURCE(S): CASREACT 125:49301; MARPAT 125:49301
GI



I

AB Quinuclidine derivs. [I; Ar = thienyl, Ph, halophenyl; R = H, C1-4 alkyl; R1 = C5-7 cycloalkyl, norbornyl, pyrrolyl, 2,3-dihydrobenzofuranyl, (alkoxy)thienyl, (hydroxy)pyridyl, quinolinyl, indolyl, (alkoxy)naphthyl, biphenyl, 2,3-methylenedioxyphenyl, substituted Ph, etc.; R2 = branched alkyl or alkenyl, C5-7 cycloalkyl, furyl, thienyl, (substituted) Ph, phenylalkyl, C1-3 alkoxy, etc.] are prepd. for use as substance P antagonists for treatment of gastrointestinal and central nervous (psychotic) disorders, inflammatory diseases, pain, and migraine. I are prepd. by redn. of the corresponding quinuclidine imine or amide. Thus, 3-keto-2-benzhydrylquinuclidine condensed with cyclohexylmethylamine to form an imine, which was reduced with 9-borabicyclononane in THF to cis-3-(cyclohexylmethylamino)-2-benzhydrylquinuclidine.

IT 129912-31-8P **129912-33-0P 129912-35-2P** 129912-37-4P
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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of quinuclidine derivs. as substance P antagonists)

IT 53898-72-9P 129912-76-1P 129912-86-3P 129912-87-4P 129912-88-5P
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135007-71-5P 135095-40-8P 177745-87-8P 177746-19-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of quinuclidine derivs. as substance P antagonists)

L7 ANSWER 17 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:306220 CAPLUS
DOCUMENT NUMBER: 125:1567
TITLE: Photoaffinity labeling of the human substance P (neurokinin-1) receptor with [3H2]azido-CP-96,345, a photoreactive derivative of a nonpeptide antagonist
AUTHOR(S): MacDonald, Douglas; Silberman, Stephen C.; Lowe, John A., III; Drozda, Susan E.; Leeman, Susan E.; Boyd, Norman D.
CORPORATE SOURCE: Dep. Pharmacol. Experimental Therapeutics, Boston Univ. Sch. Med., Boston, MA, 02118, USA
SOURCE: Molecular Pharmacology (1996), 49(5), 808-813
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An azido deriv. of [3H2](2S,3S)-cis-2-(diphenylmethyl)-N-((2-methoxyphenyl)methyl)-1-azabicyclo[2.2.2]octan-3-amine (CP-96,345), a potent nonpeptide antagonist of the substance P (SP) (neurokinin-1) receptor, was synthesized and shown to have an affinity for the human SP receptor similar to that of the parent compd., CP-96,345. When Chinese hamster ovary cells expressing the human SP receptor were photolabeled with this compd. and analyzed with the use of sodium dodecyl

sulfate-polyacrylamide gel electrophoresis and fluorog., several radioactive bands were obsd., including a major band centered at mol. mass 80 kDa, the expected value for the SP receptor expressed in Chinese hamster ovary cells. Only the labeling of the 80-kDa protein was specific: nonradiolabeled CP-96,345 but not its optical enantiomer, CP-96,344, was a potent inhibitor of photoincorporation. SP prevented photolabeling only at concns. higher than expected from its binding affinity but similar to those shown in a competition binding assay to displace a radioiodinated analog of CP-96,345. Antiserum generated against a synthetic peptide corresponding to the carboxyl terminus of the human SP receptor immunopptd. only the 80-kDa photoaffinity labeled protein, confirming that it is the human SP receptor. Interestingly, a second antiserum that was generated against the third extracellular loop of this G protein-coupled receptor no longer immunopptd. the receptor when covalently labeled with [3H2]azido-CP-96,345. This result indicates either that attachment of the antagonist modified the antigenic region directly, suggesting involvement of this domain in the binding of CP-96,345, or that the loss of recognition by the antiserum is secondary to a change in conformation induced by the covalent attachment of the antagonist at a different site.

IT **176953-35-8P**
RL: ARG (Analytical reagent use); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation); USES (Uses)
(CP-96,345 azido deriv. prepn. for antagonist photoaffinity labeling of substance P receptor)

IT **160502-78-3P 176953-36-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(CP-96,345 azido deriv. prepn. for antagonist photoaffinity labeling of substance P receptor)

L7 ANSWER 18 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:303760 CAPLUS
DOCUMENT NUMBER: 125:10619
TITLE: Preparation of substituted 3-aminoquinuclidines as substance P antagonists
INVENTOR(S): Ito, Fumitaka; Nakane, Masami; Wakabayashi, Hiroaki; Kokura, Toshihide; Satake, Kunio
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: S. African, 32 pp.
CODEN: SFXXAB
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
ZA 9203773	A	19931122	ZA 1992-3773	19920522
JP 05310735	A2	19931122	JP 1991-325237	19911113
JP 10081684	A2	19980331	JP 1997-200183	19911113
CA 2109415	AA	19921123	CA 1992-2109415	19920519
HU 65771	A2	19940728	HU 1993-3307	19920519
ES 2168260	T3	20020616	ES 1992-911350	19920519
IL 101960	A1	19990312	IL 1992-101960	19920521
CN 1068571	A	19930203	CN 1992-104860	19920522
CN 1041827	B	19990127		
US 5852038	A	19981222	US 1996-950043	19961118

PRIORITY APPLN. INFO.:
JP 1991-146826 A 19910522
JP 1991-230999 A1 19910819
JP 1991-325237 A3 19911113

US 1993-175353 A 19931220

OTHER SOURCE(S): MARPAT 125:10619
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. [I; W = (substituted) C1-6 alkyl, C2-6 alkenyl, C3-8 cycloalkyl, etc.; Ar1, Ar2, Ar3 = (substituted) Ph, naphthyl, pyridyl, etc.], useful in treatment of inflammatory diseases, anxiety, depression, pain allergies, etc., were prepd. Cyclization of piperidine-4-carboxylate II with t-BuOK followed by aldol condensation of the quinuclidine III with PhCHO, Grignard reaction of 2-benzylidene deriv. IV with PhMgBr, reaction of the 6-diphenylmethylquinuclidine V with PhCH2NH2, and redn. of the crude imine VI with NaBH(OAc)3 afforded I [W = 3-Et2NCO; Ar1 = 2,5-(MeO)2C6H3; Ar2 = Ar3 = Ph]. Compds. I are effective at 2.8-1500 mg per day.

IT **146594-93-6P 146603-61-4P 146603-68-1P**
146603-86-3P 146603-88-5P **146604-05-9P 146604-06-0P**
146604-07-1P 146604-08-2P 146604-09-3P
146604-10-6P 146604-11-7P 146604-12-8P
146604-13-9P 146682-59-9P 146682-63-5P
146682-66-8P 146682-73-7P **146682-85-1P**
146682-86-2P 146682-87-3P 146682-88-4P
146725-78-2P 146725-79-3P 152695-13-1P 152695-14-2P
152695-15-3P 152695-17-5P 152695-18-6P **157770-87-1P**
161443-36-3P 161443-37-4P 161443-38-5P
161443-39-6P 161443-40-9P 161443-41-0P
161443-42-1P 161443-43-2P 161443-44-3P
164456-77-3P 176774-32-6P 176774-33-7P
176774-38-2P 176894-11-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of substituted 3-aminoquinuclidines as substance P antagonists)

L7 ANSWER 19 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:905942 CAPLUS
DOCUMENT NUMBER: 124:86796
TITLE: Identification of a Series of 3-(Benzyloxy)-1-azabicyclo[2.2.2]octane Human NK1 Antagonists
AUTHOR(S): Swain, Christopher J.; Sewart, Eileen M.; Cascieri, Margaret A.; Fong, Tung M.; Herbert, Richard; MacIntyre, D Euan; Merchant, Kevin J.; Owen, Simon N.; Owens, Andrew P.; et al.
CORPORATE SOURCE: Neuroscience Research Centre, Merck Sharp and Dohme Research Laboratories, Harlow/Essex, CM20 2QR, UK
SOURCE: Journal of Medicinal Chemistry (1995), 38(24), 4793-805
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The synthesis and in vitro and in vivo evaluation of a series of 3-(benzyloxy)-1-azabicyclo[2.2.2]octane NK1 antagonists are described. While a no. of 3,5-disubstituted benzyl ethers afford high affinity, the 3,5-bis(trifluoromethyl)benzyl was found to combine high in vitro affinity with good oral activity. Detailed structure-activity relationship studies in conjunction with data from mol. modeling and mutagenesis work have

allowed the construction of a model of the pharmacophore. Specific interactions that have been identified include an interaction between His-197 and one of the rings of the benzhydryl, a lipophilic pocket contg. His-265 that the benzyl ether occupies, and a possible hydrogen bond between Asp-165 and the oxygen of the benzyl ether.

IT 56326-63-7P **134731-58-1P 135007-71-5P** 141958-04-5P
141958-05-6P **142035-22-1P** 144600-21-5P 144600-22-6P
144600-24-8P 144600-26-0P 144600-28-2P 144600-30-6P 144600-32-8P
144600-34-0P 144600-36-2P 144600-38-4P 144600-40-8P 144600-42-0P
144600-44-2P 144600-46-4P 144600-48-6P 144600-50-0P 144600-52-2P
144600-54-4P 144600-56-6P 144600-58-8P 144600-60-2P 144600-62-4P
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144600-84-0P 144600-86-2P 144600-88-4P 144600-92-0P 144600-96-4P
144601-13-8P 144665-79-2P 144730-90-5P 144730-91-6P 147331-34-8P
147373-67-9P 147373-68-0P 147373-71-5P 147860-62-6P
153511-59-2P 155418-46-5P 155418-47-6P 172035-53-9P
172035-54-0P 172035-55-1P 172035-56-2P **172035-60-8P**
172035-62-0P 172035-63-1P 172035-64-2P **172140-19-1P**
172140-21-5P 172140-22-6P 172140-23-7P 172140-24-8P 172140-25-9P
172140-26-0P **172140-27-1P** 172140-28-2P 172140-29-3P
172140-30-6P 172140-31-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of (benzyloxy)-1-azabicyclo[2.2.2]octane NK1 antagonists)

L7 ANSWER 20 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:791944 CAPLUS
DOCUMENT NUMBER: 123:221827
TITLE: Preparation and characterization of the tritiated NK-1 receptor antagonist CP-96.345 of a high specific radioactivity
AUTHOR(S): Kasheverov, I. E.; Zaitsev, D. A.; Utkin, Yu. N.; Tsetlin, V. I.
CORPORATE SOURCE: M. M. Shemyakin & Yu. A. Ovchinnikov Inst. Bioorganic Chem., Russian Academy Sci., Moscow, 117871, Russia
SOURCE: Bioorganicheskaya Khimiya (1994), 20(11), 1162-8
CODEN: BIKHD7; ISSN: 0132-3423
PUBLISHER: Nauka
DOCUMENT TYPE: Journal
LANGUAGE: Russian

AB [3H]CP-96.345 with the specific radioactivity of 84.2 Ci/mmol has been prepd. from CP-96.345 by the high-temp. solid state isotopic exchange. The tritiated compd. was equipotent with the parent antagonist in inhibiting the iodinated substance P binding to brain membranes from various species. Direct binding of [3H]CP-96.345 was detected by radioligand anal. using the striatum-enriched membranes from the guinea-pig brain.

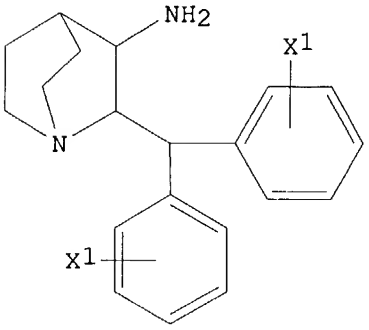
IT **135007-77-1P**
RL: ANT (Analyte); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation)
(tritiated NK-1 receptor antagonist CP-96.345 of high specific radioactivity prepn. and characterization)

L7 ANSWER 21 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:468693 CAPLUS
DOCUMENT NUMBER: 122:239552
TITLE: Preparation of optically active 3-amino-2-benzhydrylquinuclidines
INVENTOR(S): Murakami, Osamu; Kitajima, Hiroshi

PATENT ASSIGNEE(S): Yoshitomi Pharmaceutical Industries, Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 4 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 07025874	A2	19950127	JP 1993-195388	19930713

PRIORITY APPLN. INFO.: JP 1993-195388 19930713
OTHER SOURCE(S): MARPAT 122:239552
GI



I

AB Title compds. I [X1, X2 = H, halo] are prepd. reacting the resp. racemic compds. in a solvent with an optically active. (.+-.)-Cis-3-amino-2-benzhydrylquinuclidine in MeOH was heated with D-(-)-tartaric acid and then cooled to room temp. The pptd. crude crystals of (2S,3S)-3-amino-2-benzhydrylquinuclidine D-(-)-tartrate were isolated and treated with aq. NaOH and extd. with CH2Cl2 to give (2S,3S)-3-amino-2-benzhydrylquinuclidine.

IT **132746-60-2P** 162118-82-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of optically active 3-aminobenzhydrylquinuclidines)

L7 ANSWER 22 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:362481 CAPLUS
DOCUMENT NUMBER: 122:133004
TITLE: Preparation of substituted alkylbenzylaminoquinuclidines as substance P antagonists
INVENTOR(S): Satake, Kunio
PATENT ASSIGNEE(S): Pfizer Pharmaceuticals Inc., Japan; Pfizer Inc.
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

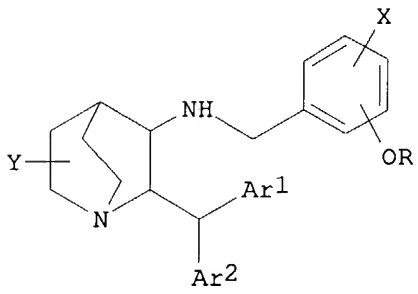
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9426740	A1	19941124	WO 1994-JP781	19940513	
W: AU, BR, CA, CN, CZ, JP, KR, NO, NZ, PL, RU, US					
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
CA 2161886	AA	19941124	CA 1994-2161886	19940513	
CA 2161886	C	19991207			
AU 9466910	A1	19941212	AU 1994-66910	19940513	
EP 699199	A1	19960306	EP 1994-914619	19940513	
EP 699199	B1	20021120			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE					
JP 08509501	T2	19961008	JP 1994-525242	19940513	
AT 228129	E	20021215	AT 1994-914619	19940513	
PT 699199	T	20030131	PT 1994-914619	19940513	
ES 2184762	T3	20030416	ES 1994-914619	19940513	
FI 9402314	A	19941120	FI 1994-2314	19940518	
US 5741797	A	19980421	US 1995-556916	19951120	

PRIORITY APPLN. INFO.: JP 1993-117102 A 19930519
WO 1994-JP781 W 19940513

OTHER SOURCE(S): MARPAT 122:133004

GI



I

AB Title compds. I (R = C1-6 alkyl; X = substituted C1-6 alkyl; Ar1, Ar2 = (substituted) aryl; Y = H, C1-6 alkyl, C2-6 alkenyl, C3-8 cycloalkyl, Z-(CH2)p, W-(CH2)m-CHR2(CH2)nR1CO wherein Z = C1-6 alkoxy, etc., p = 0-6, W = NC, HOCH2, C2-6 alkoxymethyl, etc., R1 = H, C1-6 alkyl, benzyl, (CH2)r-W, R2 = H, (substituted)C1-6 alkyl, (CH2)r-W, m, n, r = 0-3) and their salts thereof, are prepd. DDQ (oxidant) was added to 5-isopropyl-2-methoxybenzaldehyde in CH2Cl2 to give 5-(1-hydroxy-1-methylethyl)- and 5-(1-methoxy-1-methyl)-2-methoxybenzaldehyde. Na triacetoxyborohydride was added to (2S,3S)-2-(diphenylmethyl)-1-azabicyclo[2.2.2]-3-octanamine and 5-(1-hydroxy-1-methylethyl)-2-methoxybenzaldehyde in CH2Cl2 to give the title compd. (2S,3S)-N-[5-(1-hydroxy-1-methylethyl)-2-methoxyphenyl]methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]3-octanamine. The IC50 value of some I was <0.1 nM. I are also claimed for treatment of of gastrointestinal and other disorders and pharmaceutical compds. (no data).

IT **161011-07-0P 161011-08-1P 161011-09-2P**
161011-10-5P 161011-11-6P 161011-12-7P 161011-13-8P
161105-56-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of substituted alkylbenzylaminoquinuclidines as substance P antagonists)

L7 ANSWER 23 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:315540 CAPLUS
DOCUMENT NUMBER: 122:105856
TITLE: Preparation of substituted benzylamino nitrogen containing non-aromatic heterocycles and their pharmaceutical compositions as substance P receptor antagonists
INVENTOR(S): Howard, Harry R., Jr.; Ikunaka, Masaya; Ito, Fumitaka; Lowe, John A., III; Nakane, Masami; O'Neill, Brian T.; Rosen, Terry R.; Satake, Kunio
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9404496	A1	19940303	WO 1993-US4063	19930505
W: AU, BR, CA, CZ, JP, KR, NO, NZ, PL, RU, SK, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9342249	A1	19940315	AU 1993-42249	19930505
EP 655996	A1	19950607	EP 1993-910925	19930505
EP 655996	B1	20011107		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 07508755	T2	19950928	JP 1993-506227	19930505
JP 2909214	B2	19990623		
EP 1114823	A2	20010711	EP 2001-108881	19930505
EP 1114823	A3	20010718		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				
AT 208376	E	20011115	AT 1993-910925	19930505
ES 2164072	T3	20020216	ES 1993-910925	19930505
PT 655996	T	20020429	PT 1993-910925	19930505
CA 2141048	C	20030318	CA 1993-2141048	19930505
CN 1088917	A	19940706	CN 1993-109599	19930818
US 5721255	A	19980224	US 1995-387765	19950215

PRIORITY APPLN. INFO.: US 1992-932392 A2 19920819
EP 1993-910925 A3 19930505
WO 1993-US4063 W 19930505

OTHER SOURCE(S): MARPAT 122:105856
GI For diagram(s), see printed CA Issue.
AB Title compds. I [ring A is an aryl group selected from Ph, naphthyl, thienyl, dihydroquinolinyl, indolinyl; CH2NR2R3 side chain is attached to a C atom of ring A; W = H, C1-6 alkyl, S-(C1-3) alkyl, halo, C1-6 alkoxy optionally substituted with 1-3 F atoms; R1 = a variety of amino, amido, and S(O)v-contg. groups (v = 0-2), etc.; R2 = H, CO2(C1-10 alkyl); R3 = a wide variety of substituted N-contg. satd. heterocycles] are prepd. as substance P receptor antagonists. The novel compds. I are useful in the treatment of inflammatory and central nervous system disorders, as well as other disorders (no data). Included are pharmaceutical compns. for use in treatment or prevention of inflammatory diseases, anxiety, colitis, depression or dysthymic disorders, psychosis, pain, allergies, chronic obstructive airways disease, hypersensitivity disorders, vasospastic diseases, fibrosing and collagen diseases, reflex sympathetic dystrophy, addiction disorders, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathol. disorders, disorders related to immune enhancement or suppression and rheumatic disease in a mammal. Some of the 62 example compds. of the invention for which the prepns. and characterization data are described include cis-3-(5-fluoro-2-methylthiobenzyl)amino-2-phenylpiperidine dihydrochloride,

(+)-(2S,3S)-3-[2-methoxy-5-(N-isopropyl-N-methanesulfonylamino)benzyl]amin o-2-phenylpiperidine dihydrochloride, (1SR,2SR,3SR,4RS)-3-(2-methoxy-5-(N-methyl-N-methanesulfonylamino)benzyl)amino-2-benzhydryl-[2.2.1]azanorbornane dihydrochloride, and (2S,3S)-N-(2-methoxy-5-methylthiophenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine mesylate.

IT 14665-72-6P 19434-34-5P, 2-Phenoxybenzaldehyde 55845-76-6P
67868-81-9P 91827-45-1P 136871-75-5P 142035-23-2P 145876-88-6P
156603-16-6P **160502-74-9P** 160503-31-1P 160503-32-2P
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160503-53-7P 160503-54-8P 160503-55-9P 160503-56-0P 160503-57-1P
160503-58-2P 160503-73-1P 160503-74-2P 160503-75-3P 160503-76-4P
160503-77-5P 160503-78-6P 160503-79-7P **160551-68-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reaction of, in prepn. of substance P receptor antagonist)

IT 145741-93-1P 145741-94-2P 145741-95-3P 145741-96-4P 145877-16-3P
160502-36-3P 160502-37-4P 160502-38-5P 160502-39-6P 160502-40-9P
160502-41-0P 160502-42-1P 160502-43-2P 160502-44-3P 160502-45-4P
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160502-94-3P **160502-95-4P 160502-96-5P**
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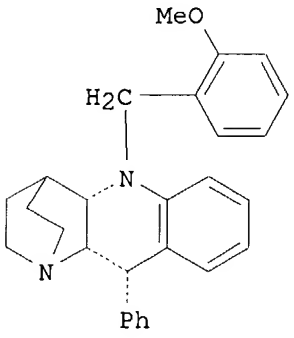
160503-69-5P 160503-70-8P 160503-71-9P 160503-72-0P 160551-64-4P
160551-65-5P 160551-66-6P **160551-67-7P**
160551-69-9P 160551-70-2P 160551-71-3P
160551-73-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as substance P receptor antagonist)

L7 ANSWER 24 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:46409 CAPLUS
DOCUMENT NUMBER: 122:9904
TITLE: Synthesis of a benzo[b]-1,5-naphthyridine derivative as a potential constrained NK1 receptor antagonist
AUTHOR(S): Viti, Giovanni; Giannotti, Danilo; Nannicini, Rossano; Balacco, Giuseppe; Pestellini, Vittorio
CORPORATE SOURCE: Chem. Res. Dep., Firenze, 50131, Italy
SOURCE: Tetrahedron Letters (1994), 35(32), 5939-42
CODEN: TELEAY; ISSN: 0040-4039
DOCUMENT TYPE: Journal

LANGUAGE: English
OTHER SOURCE(S): CASREACT 122:9904
GI



I

AB A short synthesis of a cyclic constrained analog I of the potent Substance P antagonist (.+-.)-CP-96345 is described. The key feature is the formation of the benzo[b]-1,5-naphthyridine system at the very last step of the synthesis through an intramol. arylation of an amine promoted by a strong base. If the tricyclic system was synthesized first, 2-methoxybenzylation of both the nitrogen atoms occurred.

IT 21820-08-6P 159553-05-6P 159553-07-8P **159553-08-9P** 159553-09-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of a benzo[b]-1,5-naphthyridine deriv.)

L7 ANSWER 25 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:645102 CAPLUS
DOCUMENT NUMBER: 121:245102
TITLE: N-alkyl quinuclidinium substance P antagonists
AUTHOR(S): Lowe, John A., III; Drozda, Susan E.; McLean, Stafford; Crawford, Rosemary T.; Bryce, Dianne K.; Bordner, Jon
CORPORATE SOURCE: Cent. Res. Div., Pfizer Inc., Groton, CT, 06340, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (1994), 4(9), 1153-6
CODEN: BMCLE8; ISSN: 0960-894X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The synthesis and structure-activity relationship of bridgehead N-alkylated analogs of the nonpeptide substance P antagonist CP-96,345 are described. The results indicate that the bridgehead nitrogen may provide more of an anchoring function rather than being in intimate contact with the receptor.

IT 49623-78-1DP, Quinuclidinium, alkyl derivs. **132746-60-2P**, CP 96345 158548-00-6P 158548-01-7P 158548-02-8P 158548-03-9P 158548-04-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and structure-activity relationship of, as nonpeptide substance P antagonist)

L7 ANSWER 26 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:508556 CAPLUS

DOCUMENT NUMBER: 121:108556
TITLE: Preparation of substituted benzylaminoquinuclidines as substance P antagonists
INVENTOR(S): Ito, Fumitaka; Satake, Kunio; Shimada, Kaoru
PATENT ASSIGNEE(S): Pfizer Inc., Japan
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9408997	A1	19940428	WO 1993-US9168	19930930
W: AU, CA, KR, NO, NZ, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
JP 06135963	A2	19940517	JP 1992-283135	19921021
CA 2146259	AA	19940428	CA 1993-2146259	19930930
CA 2146259	C	19980407		
AU 9351653	A1	19940509	AU 1993-51653	19930930
EP 665844	A1	19950809	EP 1993-922754	19930930
EP 665844	B1	20000906		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
AT 196140	E	20000915	AT 1993-922754	19930930
ES 2149215	T3	20001101	ES 1993-922754	19930930
PT 665844	T	20010131	PT 1993-922754	19930930
FI 9304626	A	19940422	FI 1993-4626	19931020
HU 65133	A2	19940428	HU 1993-2965	19931020
ZA 9307780	A	19950420	ZA 1993-7780	19931020
US 5604241	A	19970218	US 1995-416913	19950420
GR 3034498	T3	20001229	GR 2000-402187	20000928

PRIORITY APPLN. INFO.: JP 1992-283135 A 19921021
WO 1993-US9168 W 19930930
OTHER SOURCE(S): MARPAT 121:108556
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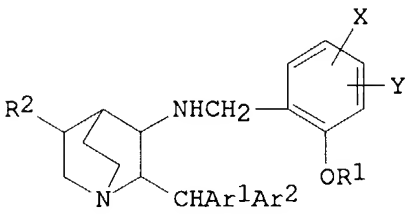

I

AB Title compds. I (Ar1, Ar2 = (substituted) aryl; R1 = C1-6 alkyl; R2 = H, C1-6 alkyl; X, Y = H, dialkylphosphoryl having 2-12 carbons, alkyl having 1-6 carbons, alkenyl having 2-6 carbons, alkynyl having 2-6 carbons; XY = 3-5 hydrocarbyl, optionally contg. >2 double bonds and optionally having 1-2 substituents, provided that when X and Y are taken together they are attached to adjacent carbons, and provided that if either X or Y is H, then the other one is alkenyl or alkynyl) or a salt thereof, as substance P antagonists (no data), are prepd. I are claimed for treatment of gastrointestinal and CNS disorders, and alleviation of inflammatory disease, asthma, pain or migraine. Tri-n-butylisopropenylltin in MePh was added to 5-bromo-o-anisaldehyde, Pd(PPh3)4 and 2,6-di-tert-butyl-4-methylphenol in MePh to give 5-isopropenyl-o-anisaldehyde which was treated with (-)-(2S,3S)-cis-2-(diphenylmethyl)-1-azabicyclo[2.2.2]octan-3-

amine and NaBH(OAc)3 in CH2Cl2 to give (2S,3S)-I (Ar1 = Ar2 = Ph, R1 = Me, R2 = Y = H, X = 5-CH2:CMe).

IT **156749-85-8P 156749-86-9P 156749-87-0P**
156749-88-1P 156749-89-2P 156749-90-5P **156749-91-6P**
156749-92-7P 156749-93-8P 156854-51-2P
156854-52-3P 156854-53-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as substance P antagonist)

L7 ANSWER 27 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:508540 CAPLUS
DOCUMENT NUMBER: 121:108540
TITLE: Preparation of (2S,3S)-N-(5-propyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine as a substance P antagonist
INVENTOR(S): Ito, Fumitaka; Kondo, Hiroshi; Nakane, Masami; Shimada, Kaoru
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9411368	A1	19940526	WO 1993-US6624	19930719
W: AU, CA, JP, KR, NO, NZ, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2149242	AA	19940526	CA 1993-2149242	19930719
CA 2149242	C	19980804		
AU 9346780	A1	19940608	AU 1993-46780	19930719
AU 676489	B2	19970313		
EP 668863	A1	19950830	EP 1993-917176	19930719
EP 668863	B1	19970108		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 07508731	T2	19950928	JP 1993-502707	19930719
AT 147385	E	19970115	AT 1993-917176	19930719
ES 2096312	T3	19970301	ES 1993-917176	19930719
IL 107495	A1	19981227	IL 1993-107495	19931104
FI 9304983	A	19940513	FI 1993-4983	19931111
CN 1091134	A	19940824	CN 1993-114371	19931111
CN 1034732	B	19970430		
ZA 9308421	A	19950511	ZA 1993-8421	19931111
NO 9501865	A	19950511	NO 1995-1865	19950511
US 5886009	A	19990323	US 1995-500958	19950619
PRIORITY APPLN. INFO.:			US 1992-975244	19921112
			WO 1993-US6624	19930719

AB (2S,3S)-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine was reductively condensed with 5-propyl-2-methoxybenzaldehyde to give the title compd. as a substance P antagonist (no data).

IT **156640-71-0P 156640-72-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as substance P antagonist)

L7 ANSWER 28 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:508539 CAPLUS
DOCUMENT NUMBER: 121:108539
TITLE: Substituted quinuclidines as substance P antagonists
INVENTOR(S): Ito, Fumitaka; Kokura, Toshihide; Nakane, Masami; Satake, Kunio; Wakabayashi, Hiroaki
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9410170	A1	19940511	WO 1993-US9169	19930930
W: AU, CA, KR, NO, NZ, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
JP 06135964	A2	19940517	JP 1992-290569	19921028
CA 2146007	AA	19940511	CA 1993-2146007	19930930
CA 2146007	C	19990223		
AU 9351412	A1	19940524	AU 1993-51412	19930930
EP 665843	A1	19950809	EP 1993-922406	19930930
EP 665843	B1	20030813		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
AT 247113	E	20030815	AT 1993-922406	19930930
PT 665843	T	20031231	PT 1993-922406	19930930
ES 2202313	T3	20040401	ES 1993-922406	19930930
FI 9304752	A	19940429	FI 1993-4752	19931027
HU 65831	A2	19940728	HU 1993-3051	19931027
US 5837711	A	19981117	US 1995-428240	19950428

PRIORITY APPLN. INFO.: JP 1992-290569 A 19921028
WO 1993-US9169 W 19930930
OTHER SOURCE(S): MARPAT 121:108539
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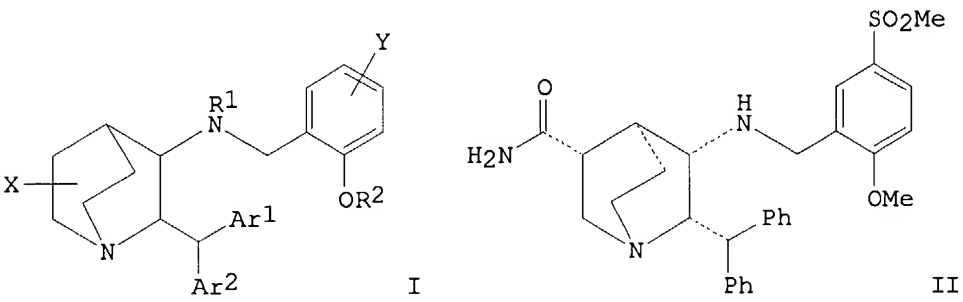


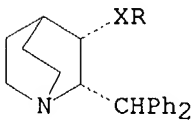
AB Disclosed are quinuclidines with the ability to antagonize substance P, and having formula I [Ar1, Ar2 = thienyl, Ph, fluorophenyl, chlorophenyl or bromophenyl; X = CONR3R4, CO2R3, CH2OR3, CH2NR3R4 or CONR3OR4; R1, R3, R4 = H, C1-4 alkyl; R2 = C1-4 alkyl; Y = alkylsulfonyl, alkylalkanoylamino, alkyl(haloalkanoyl)amino, alkyl(alkylsulfonyl)amino, alkyl(haloalkylsulfonyl)amino, alkenyl, alkynyl, haloalkyl, alkylamino, alkanoylamino, (haloalkanoyl)amino, (haloalkylsulfonyl)amino]. I are useful in the treatment of gastrointestinal or central nervous system disorders, and the alleviation of inflammatory diseases, asthma, pain, and migraine in mammals (no data). Some preferred compds. are said to have

shown IC50 values of 0.1-1.9 nM for inhibition of substance P binding at its receptors in std. assays. For example, 5-bromo-o-anisaldehyde underwent conversion to its ethylene acetal (88.3%), conversion of the bromide function to methylthio (77.2%), hydrolysis to the aldehyde (86.7%), and S-oxidn., to give 5-methylsulfonyl-o-anisaldehyde. This underwent reductive amination by (3R,4S,5S,6S)-5-amino-6-diphenylmethyl-1-azabicyclo[2.2.2]octane-3-carboxamide and NaBH(OAc)3 to give 58.2% title compd. II as its di-HCl salt.

IT **146604-12-8P 156603-22-4P 156603-23-5P 156603-24-6P 156603-25-7P 156713-57-4P 156713-58-5P 156713-59-6P 156713-60-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as substance P antagonist)

L7 ANSWER 29 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1994:457282 CAPLUS
DOCUMENT NUMBER: 121:57282
TITLE: Quinuclidine-based NK-1 antagonists I: 3-benzyloxy-1-azabicyclo[2.2.2]octanes
AUTHOR(S): Seward, Eileen M.; Swain, Christopher J.; Merchant, Kevin J.; Owen, Simon N.; Sabin, Verity; Cascieri, Margaret A.; Sadowski, Sharon; Strader, Catherine; Baker, Raymond
CORPORATE SOURCE: Neurosci. Res. Cent., Merck Sharp Dohme Res. Lab., Harlow/Essex, CM20 2QR, UK
SOURCE: Bioorganic & Medicinal Chemistry Letters (1993), 3(6), 1361-6
CODEN: BMCLE8; ISSN: 0960-894X
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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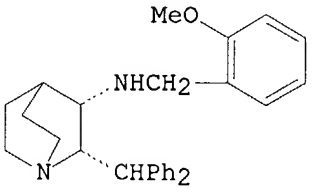

II

AB Analogs I [R = Ph, X = NHCH2, NHCH2CH2, NHCO, OCO, etc.; RX = (un)substituted benzyloxy] of CP-96,345 (II) were prepd. and their affinity for the human NK1 receptor tested. The 3-benzyloxy derivs. had significant affinity for the human NK1 receptor. 3,5-Disubstitution of the benzyl ether has been identified to be essential for high affinity.

IT **132746-60-2DP**, CP-96,345, analogs **155618-00-1P** 155618-01-2P 155618-02-3P 155618-03-4P 155618-04-5P 155618-05-6P 155618-06-7P **155681-48-4P** 155681-49-5P 155681-50-8P 155681-51-9P 155681-52-0P 155681-53-1P 155681-54-2P 155681-55-3P 155681-56-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and NK-1 antagonist activity of)

L7 ANSWER 30 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1994:322931 CAPLUS
DOCUMENT NUMBER: 120:322931
TITLE: 2-Step formylation process for preparation of (methoxy)benzaldehydes
INVENTOR(S): Godek, Dennis M.; Synder, William M.; Stewart, Andrew M.
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: U.S., 7 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5294744	A	19940315	US 1993-49904	19930420
WO 9424081	A1	19941027	WO 1994-US445	19940126
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2160686	AA	19941027	CA 1994-2160686	19940126
CA 2160686	C	19980106		
EP 690835	A1	19960110	EP 1994-906619	19940126
EP 690835	B1	19980819		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 08505399	T2	19960611	JP 1994-523111	19940126
JP 2745163	B2	19980428		
AT 169896	E	19980915	AT 1994-906619	19940126
ES 2119171	T3	19981001	ES 1994-906619	19940126
FI 9401808	A	19941021	FI 1994-1808	19940419

PRIORITY APPLN. INFO.: US 1993-49904 19930420
WO 1994-US445 19940126
OTHER SOURCE(S): CASREACT 120:322931; MARPAT 120:322931
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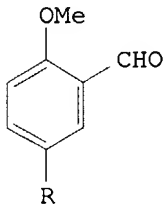

I

AB The title compds. (I; R = CHMe2, OCF3), useful as intermediates in the prepn. of substance P receptor antagonists, are prepd. by reacting the corresponding 4-substituted phenol with a di-Me carbonate in the presence of a tertiary-amine base [e.g., 4-(dimethylamino)pyridine] optionally in the presence of an inert, polar, org. solvent (i.e., the solvent is always present when R = CHMe2) at 120-170.degree. to form the corresponding 4-substituted anisoles which are reacted within the 2nd step with hexamethylenetetramine in the presence of F3CO2H at temps. of 65.degree. to the reflux temp. of the reaction mixt.

IT 145742-28-5P **147116-64-1P 147780-91-4P** 155018-94-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as substance P receptor antagonist)

L7 ANSWER 31 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:106787 CAPLUS
DOCUMENT NUMBER: 120:106787
TITLE: Preparation of quinuclidinecarboxamides as substance P antagonists
INVENTOR(S): Satake, Kunio; Wakabayashi, Hiroaki; Nakane, Masami
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9319064	A1	19930930	WO 1993-US1810	19930305
W: AU, CA, FI, HU, KR, NO, NZ, PL, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
JP 05320162	A2	19931203	JP 1992-307179	19921117
AU 9337824	A1	19931021	AU 1993-37824	19930305
EP 632809	A1	19950111	EP 1993-907099	19930305
EP 632809	B1	20010905		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
CA 2132541	C	19971125	CA 1993-2132541	19930305
AT 205207	E	20010915	AT 1993-907099	19930305
ES 2160596	T3	20011116	ES 1993-907099	19930305
PT 632809	T	20011228	PT 1993-907099	19930305
ZA 9302016	A	19940922	ZA 1993-2016	19930322
FI 9404394	A	19940922	FI 1994-4394	19940922
NO 9403526	A	19940922	NO 1994-3526	19940922
US 5569662	A	19961029	US 1994-313289	19941003
GR 3037025	T3	20020131	GR 2001-401896	20011025

PRIORITY APPLN. INFO.: JP 1992-65337 A 19920323
WO 1993-US1810 A 19930305
OTHER SOURCE(S): MARPAT 120:106787
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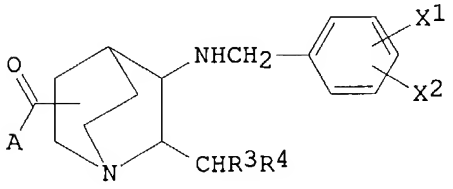

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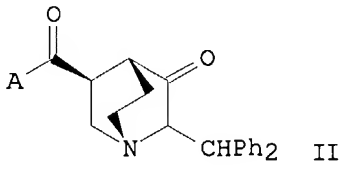

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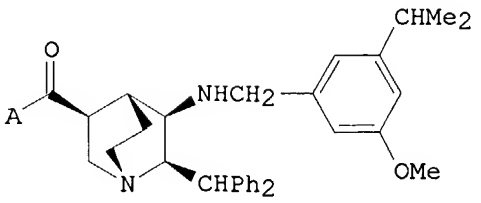


III

AB Title compds. [I; A = NR1(CH2)nCHR2(CH2)mY; R1 = H, alkyl, CH2Ph, (CH2)pY; R2 = groups cited for R1, 3-indolylmethyl, etc.; R1R2 = atoms to form a

ring; R3, R4 = thienyl, C6H4R; R = H, F, Cl, Br; X1 = (halo)alkoxy; X2 = H, halo, alkyl, alkoxy, etc.; Y = cyano, COZ, CH2Z; Z = OH, alkoxy, (di)(alkyl)amino; m, n, p = 0-3] were prepd. Thus, N,N-diethyl-4-methoxycarbonyl-1-methoxycarbonylmethylpiperidine-3-carboxamide was cyclized and the product converted in 6 steps to quinuclidinonecarboxamide II (A = NACH2CO2NH2) which was reductively condensed with 5-isopropyl-2-methoxybenzylamine to give, after sapon., title compd. III.2HCl (A = NHCH2CO2H). Selected I had IC50 <0.1 nM against substance P binding in vitro.

IT **152567-49-2P 152567-50-5P 152567-51-6P**
152567-52-7P 152567-53-8P 152567-54-9P
152567-55-0P 152567-56-1P 152567-57-2P
152567-58-3P 152567-59-4P 152567-60-7P
152567-61-8P 152567-62-9P 152695-07-3P
152695-08-4P 152695-09-5P 152695-10-8P
152695-11-9P 152695-12-0P 152782-83-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as substance P antagonist)

L7 ANSWER 32 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:100753 CAPLUS
DOCUMENT NUMBER: 120:100753
TITLE: Radioiodinated L-703,606: a potent, selective antagonist to the human NK1 receptor
AUTHOR(S): Francis, B. E.; Swain, C.; Sabin, V.; Burns, H. D.
CORPORATE SOURCE: Dep. Radiopharmacol., Merck Res. Lab., West Point, PA, 19486, USA
SOURCE: Applied Radiation and Isotopes (1994), 45(1), 97-103
CODEN: ARISEF; ISSN: 0883-2889
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new, radioiodinated, NK1 selective radiotracer ([125I]L-703,606) was prepd. L-703,606 Is an iodinated analog of the NK1 antagonist CP-96,345 in which the methoxy group has been replaced by an iodine substituent. [125I]L-703,606 was made from the corresponding trimethylsilyl compd. by treatment with no carrier added Na125I and an Iodobead in TFA. The tracer was prepd. at a specific activity of .apprx.1100 Ci/mmol and preliminary binding studies demonstrated that [125I]L-703,606 binds selectively to NK1 receptors with a kd = 0.3 nM. These results suggest that this radioligand will be useful for the biochem. and pharmacol. characterization of the human NK1 receptor and, if labeled with 123I, may be useful for noninvasive NK1 receptor imaging via SPECT.

IT **144425-84-3P**, l 703606
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and radioiodination of)

IT **152827-49-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of and NK1 receptor binding by, SPECT in relation to)

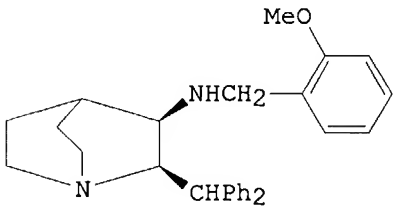
L7 ANSWER 33 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:576738 CAPLUS
DOCUMENT NUMBER: 119:176738
TITLE: Synthesis of a nonpeptide carbon-11 labeled substance P antagonist for PET studies
AUTHOR(S): Del Rosario, Renato B.; Mangner, Thomas J.; Gildersleeve, David L.; Shreve, Paul D.; Wieland, Donald M.; Lowe, John A., III; Drozda, Susan E.; Snider, Michael

CORPORATE SOURCE: Med. Cent., Univ. Michigan, Ann Arbor, MI, 48109-0028, USA
SOURCE: Nuclear Medicine and Biology (1993), 20(4), 545-7
CODEN: NMBIEO; ISSN: 0883-2897
DOCUMENT TYPE: Journal
LANGUAGE: English

AB CP 96,345 is a nonpeptide high affinity antagonist of the substance P (NK1) receptor. The radiosynthesis of [11C]CP 96,345 suitable for positron emission tomog. (PET) applications is described. [11C]CP 96,345 was prepd. by O-methylation of a desmethyl precursor via in situ generation of its phenolate salt. The in vivo tissue distribution of [11C]CP 96,345 in guinea pigs (n = 2) at 5 and 30 min was detd. Uptake was low in brain (.apprxeq.0.04% dose/g) and highest (.apprxeq.1-2% dose/g) in the spleen and lungs. The present findings indicate that the use of [11C]CP 96,345 in PET might be more applicable to the study of substance P receptors in peripheral tissues involved with inflammatory disease and arthritis.

IT **150326-26-4P**
RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(prepn. and metab. of, PET of substance P receptors in brain in relation to)

L7 ANSWER 34 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:539026 CAPLUS
DOCUMENT NUMBER: 119:139026
TITLE: An SAR study for the non-peptide substance P receptor (NK1) antagonist, CP-96,345
AUTHOR(S): Howson, William; Hodgson, Julie; Richardson, Reg; Walton, Lesley; Guard, Steve; Watling, Keith
CORPORATE SOURCE: Parke-Davis Neurosci. Res. Cent., Cambridge, CB2 2QB, UK
SOURCE: Bioorganic & Medicinal Chemistry Letters (1992), 2(6), 559-64
CODEN: BMCLE8; ISSN: 0960-894X
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Results for an SAR study around the novel, non-peptide substance P receptor NK1 antagonist, (.+-.)CP-96,345 (I) are described. The prepns. are described. The importance of the 2.degree. nitrogen and the arom. moieties are clarified.

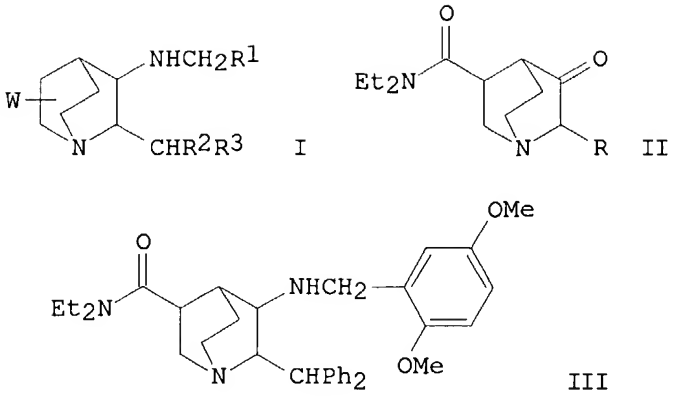
IT 32531-19-4P **129912-33-0P 129912-47-6P**
129912-52-3P 134731-58-1P 135007-71-5P
135007-72-6P 142035-22-1P 147331-34-8P 149454-08-0P
149454-09-1P **149454-10-4P** 149454-11-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and P receptor (NK1) antagonist activity of)

L7 ANSWER 35 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:495339 CAPLUS
DOCUMENT NUMBER: 119:95339
TITLE: Preparation of 6-benzhydryl-5-benzylamino-1-azabicyclo[2.2.2]octane-3-carboxylates and analogs as substance P antagonists
INVENTOR(S): Ito, Fumitaka; Kokura, Toshihide; Nakane, Masami; Satake, Kunio; Wakabayashi, Hiroaki
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: PCT Int. Appl., 101 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9220676	A1	19921126	WO 1992-US4002	19920519
W: AU, BR, CA, CS, DE, FI, HU, KR, NO, PL, RU, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE				
JP 05310735	A2	19931122	JP 1991-325237	19911113
JP 10081684	A2	19980331	JP 1997-200183	19911113
CA 2109415	AA	19921123	CA 1992-2109415	19920519
AU 9219275	A1	19921230	AU 1992-19275	19920519
AU 658898	B2	19950504		
EP 585328	A1	19940309	EP 1992-911350	19920519
EP 585328	B1	20020109		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
HU 65771	A2	19940728	HU 1993-3307	19920519
BR 9206044	A	19950301	BR 1992-6044	19920519
PL 170513	B1	19961231	PL 1992-301418	19920519
PL 170525	B1	19961231	PL 1992-311527	19920519
PL 171921	B1	19970630	PL 1992-311526	19920519
PL 172069	B1	19970731	PL 1992-311525	19920519
RU 2092486	C1	19971010	RU 1993-58351	19920519
AT 211743	E	20020115	AT 1992-911350	19920519
ES 2168260	T3	20020616	ES 1992-911350	19920519
IL 101960	A1	19990312	IL 1992-101960	19920521
CN 1068571	A	19930203	CN 1992-104860	19920522
CN 1041827	B	19990127		
NO 9304195	A	19931119	NO 1993-4195	19931119
US 5716965	A	19980210	US 1993-175353	19931220
US 5852038	A	19981222	US 1996-950043	19961118

PRIORITY APPLN. INFO.:
JP 1991-146826 A 19910522
JP 1991-230999 A1 19910819
JP 1991-325237 A3 19911113
WO 1992-US4002 A 19920519
US 1993-175353 A 19931220

OTHER SOURCE(S): MARPAT 119:95339
GI



I II III

AB Title compds. [I; R1-R3 - (substituted)Ph, -pyridyl, -imidazolyl, etc.; W - (Cyclo)alkyl, alkoxy, CONH2, CO2N, etc.] were prepd. as substance P antagonists (no data). Thus, cis-Me 3-diethylcarbamoyl-1-(methoxycarbonylmethyl)piperidine-4-carboxylate (prepn. ref. given) was cyclized to give oxobicyclooctanecarboxamide (3R,4R)-II (R = H) which was condensed with PhCHO and the product condensed with PhMgBr to give (3R,4R,6S)- and (3R,4R,6R)-II (R = CHPh2). These were condensed with 2,5-(MeO)2C6H3CH2NH2 and the product reduced by NaBH(OAc)3 to give title compd. (3R,4R,5S,6S)-III.

IT **146594-86-7P 146594-87-8P 146594-88-9P**
146594-89-0P 146594-90-3P 146594-91-4P
146594-92-5P 146594-93-6P 146594-94-7P
146594-95-8P 146594-96-9P 146594-97-0P
146594-98-1P 146594-99-2P 146595-00-8P
146595-01-9P 146603-59-0P 146603-60-3P
146603-61-4P 146603-62-5P 146603-63-6P
146603-64-7P 146603-65-8P 146603-66-9P
146603-67-0P 146603-68-1P 146603-69-2P
146603-70-5P 146603-71-6P 146603-72-7P
146603-73-8P 146603-74-9P 146603-75-0P
146603-76-1P 146603-77-2P 146603-78-3P
146604-05-9P 146604-06-0P 146604-07-1P
146604-08-2P 146604-09-3P 146604-10-6P
146604-11-7P 146604-12-8P 146604-13-9P
146682-57-7P 146682-58-8P 146682-59-9P
146682-60-2P 146682-61-3P 146682-62-4P
146682-63-5P 146682-64-6P 146682-65-7P
146682-66-8P 146682-67-9P 146682-68-0P
146682-69-1P 146682-70-4P 146682-71-5P
146682-79-3P 146682-80-6P 146682-81-7P
146682-82-8P 146682-83-9P 146682-84-0P
146682-85-1P 146682-86-2P 146682-87-3P
146682-88-4P 146725-78-2P 146725-79-3P
146935-74-2P 146987-69-1P 146987-71-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as substance P antagonist)

L7 ANSWER 36 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:254758 CAPLUS
DOCUMENT NUMBER: 118:254758
TITLE: Preparation of 3-[(fluoroalkoxy)benzylamino]piperidine

s and analogs as substance P antagonists
INVENTOR(S): Lowe, John Adams, III; Rosen, Terry Jay
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9300331	A1	19930107	WO 1992-US3571	19920505
W: AU, BR, CA, CS, DE, FI, HU, JP, KR, NO, PL, RU, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE				
CA 2109613	AA	19930107	CA 1992-2109613	19920505
CA 2109613	C	19961119		
AU 9218893	A1	19930125	AU 1992-18893	19920505
AU 657967	B2	19950330		
EP 589924	A1	19940406	EP 1992-911210	19920505
EP 589924	B1	19960904		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 06506473	T2	19940721	JP 1992-510950	19920505
JP 07110850	B4	19951129		
HU 70499	A2	19951030	HU 1995-836	19920505
BR 9206161	A	19951031	BR 1992-6161	19920505
AT 142199	E	19960915	AT 1992-911210	19920505
ES 2092113	T3	19961116	ES 1992-911210	19920505
PL 170516	B1	19961231	PL 1992-310851	19920505
PL 172054	B1	19970731	PL 1992-301884	19920505
RU 2114848	C1	19980710	RU 1993-58531	19920505
SK 282203	B6	20011203	SK 1992-3908	19920505
CZ 290475	B6	20020717	CZ 1992-3908	19920505
IL 102188	A1	20021201	IL 1992-102188	19920612
ZA 9204528	A	19921220	ZA 1992-4528	19920619
CN 1067655	A	19930106	CN 1992-104778	19920619
CN 1056373	B	20000913		
US 5773450	A	19980630	US 1993-167881	19931214
NO 9304691	A	19931217	NO 1993-4691	19931217
NO 180715	B	19970224		
NO 180715	C	19970604		
HU 67434	A2	19950428	HU 1993-3668	19931220
US 2003199540	A1	20031023	US 2003-379198	20030304

PRIORITY APPLN. INFO.:

US 1991-717943	A2	19910620
WO 1992-US3571	A	19920505
US 1993-167881	A3	19931214
HU 1993-3668	A	19931220
US 1998-7268	A1	19980114

OTHER SOURCE(S): MARPAT 118:254758
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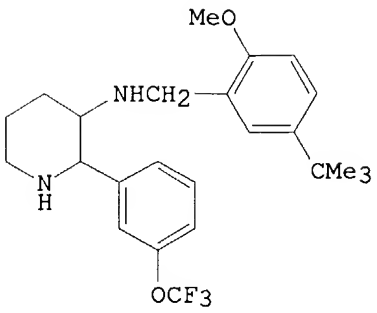

I

AB Title compds., e.g., X1X2X3C6H2CH2NHR [R = aza(bi)cycloalkyl, etc.; X1 = H, (fluoro)alkyl, -alkoxy; X2, X3 = H, halo, NO2, (fluoro)alkyl, -alkoxy, etc.] were prepd. as substance P antagonists (no data). Thus, 3-(F3CO)C6H4CHO was cyclocondensed with O2N(CH2)3CO2Me and AcNH4 and the product reduced to give cis-5-amino-6-(3-trifluoromethoxyphenyl)piperidin-2-one which was reductively condensed with 2,5-(MeO)(Me3C)C6H3CHO to give, after keto group redn., title compd. cis-I.

IT 145741-98-6P 145741-99-7P 145742-00-3P 145742-01-4P 145742-02-5P
145742-17-2P 145742-18-3P 145742-19-4P 145742-21-8P 145742-22-9P
145742-23-0P 145742-25-2P 145742-26-3P 145742-28-5P 145742-29-6P
145742-30-9P 145742-31-0P 145742-33-2P 145742-69-4P 145877-22-1P
145877-23-2P 145877-24-3P 145877-25-4P 145877-27-6P 145877-45-8P
145877-46-9P 145877-47-0P 145877-49-2P 145877-50-5P 145877-52-7P
145877-53-8P 145877-54-9P 145877-57-2P 147231-98-9P 147231-99-0P
147232-00-6P 147232-01-7P 147232-02-8P 147232-03-9P 147232-04-0P
147249-22-7P 147249-23-8P **147249-24-9P** 147249-25-0P
147249-26-1P **147852-80-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as substance P antagonist)

L7 ANSWER 37 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:254756 CAPLUS
DOCUMENT NUMBER: 118:254756
TITLE: Preparation of 2-diphenylmethyl-3-benzylaminoquinuclidines as substance P antagonists
INVENTOR(S): Ito, Fumitaka; Kondo, Hiroshi; Shimada, Kaoru; Nakane, Masami; Lowe, John Adams, III; Rosen, Terry Jay; Yang, Bingwei Vera
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9221677	A1	19921210	WO 1992-US3317	19920428
W: AU, BG, BR, CA, CS, DE, FI, HU, JP, KR, NO, PL, RO, RU, US				
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GN, GR, IT, LU, MC, ML, MR, NL, SE, SN, TD, TG				
AU 9219901	A1	19930108	AU 1992-19901	19920428
AU 657552	B2	19950316		

EP 587723	A1	19940323	EP 1992-912601	19920428
EP 587723	B1	19960306		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 06504292	T2	19940519	JP 1992-500353	19920428
JP 07033386	B4	19950412		
BR 9206073	A	19941206	BR 1992-6073	19920428
HU 70151	A2	19950928	HU 1993-3393	19920428
RO 110499	B1	19960130	RO 1993-1581	19920428
AT 135006	E	19960315	AT 1992-912601	19920428
ES 2084361	T3	19960501	ES 1992-912601	19920428
CZ 281403	B6	19960911	CZ 1992-3906	19920428
PL 171379	B1	19970430	PL 1992-301472	19920428
RU 2103269	C1	19980127	RU 1993-58555	19920428
SK 278788	B6	19980204	SK 1992-3906	19920428
CA 2102179	C	19981027	CA 1992-2102179	19920428
IN 178484	A	19970503	IN 1992-DE384	19920504
IL 102008	A1	19951208	IL 1992-102008	19920526
ZA 9203942	A	19931129	ZA 1992-3942	19920529
CN 1067428	A	19921230	CN 1992-104129	19920530
CN 1048492	B	20000119		
NO 9304312	A	19931129	NO 1993-4312	19931129
US 5807867	A	19980915	US 1994-211120	19940523
JP 07285965	A2	19951031	JP 1994-241456	19941005
JP 2645225	B2	19970825		
US 6222038	B1	20010424	US 1995-377552	19950124

PRIORITY APPLN. INFO.: US 1991-708404 A2 19910531
WO 1992-US3317 A 19920428
US 1994-211120 A3 19940523

OTHER SOURCE(S): MARPAT 118:254756

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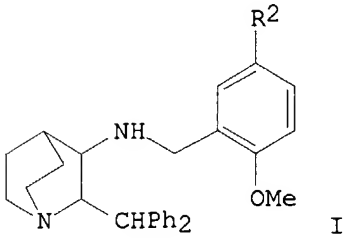


I

AB Title compds. (I; R2 = Me2CH, Me3C, Me, Et, sec-Bu), were prepd. as substance P antagonists useful against a variety of diseases (no data). Thus, (2S, 3S)-2-diphenylmethyl-1-azabicyclo[2.2.2]-octane-3-amine (prepn. given) was stirred with 5-isopropyl-2-methoxybenzaldehyde and Na triacetoxyborohydride in CH2Cl2 to give 2S,3S-I (R2 = Me2CH).

IT **147116-64-1P 147116-65-2P 147116-66-3P**
147116-67-4P 147116-68-5P 147780-91-4P
147780-92-5P 147780-93-6P 147780-94-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as substance P antagonist)

L7 ANSWER 38 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:147434 CAPLUS
DOCUMENT NUMBER: 118:147434

TITLE: Discovery of a potent substance P antagonist: recognition of the key molecular determinant
AUTHOR(S): Desai, Manoj C.; Lefkowitz, Sheri L.; Thadeio, Peter F.; Longo, Kelly P.; Snider, R. Michael
CORPORATE SOURCE: Cent. Res. Div., Pfizer Inc., Groton, CT, 06340, USA
SOURCE: Journal of Medicinal Chemistry (1992), 35(26), 4911-13
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 118:147434
AB The specific geometrical parameters that make the design of further substance P antagonists (human IM-9 cell) more facile is disclosed. (+)-(2S,3S)-(2-Methoxybenzylamino)-2-phenylpiperidine (I, CO-99,994), is the most potent SP antagonist yet discovered and that the biol. activity resides exclusively in (+)-(2S,3S)-I. (+)-I was found upon anal. and prediction of the important structural requirements for receptor binding. An enantiospecific synthesis of (+)-(2S,3S)-I is described.
IT **132746-60-2P 134731-58-1P** 136870-97-8P 136871-18-6P 136982-36-0P, CP 99994 136982-37-1P 145148-39-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and in vitro binding affinity of, with substance P antagonist)

L7 ANSWER 39 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:80779 CAPLUS
DOCUMENT NUMBER: 118:80779
TITLE: The discovery of (2S,3S)-cis-2-(diphenylmethyl)-N-[(2-methoxyphenyl)methyl]-1-azabicyclo[2.2.2]octan-3-amine as a novel, nonpeptide substance P antagonist. [Erratum to document cited in CA117(5):48289n]
AUTHOR(S): Lowe, John A., III; Drozda, Susan E.; Snider, R. Michael; Longo, Kelly P.; Zorn, Stevin H.; Morrone, Jean; Jackson, Elisa R.; McLean, Stafford; Bryce, Dianne K.; et al.
CORPORATE SOURCE: Cent. Res. Div., Pfizer, Inc., Groton, CT, 06340, USA
SOURCE: Journal of Medicinal Chemistry (1992), 35(25), 4768
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An error in Compd. 12 has been cor. The error was not reflected in the abstr. or the index entries.
IT **141957-92-8P**
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and crystal structure of (Erratum))
IT **135007-73-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and debenzylation of (Erratum))
IT **132746-60-2P 135007-72-6P 141957-93-9P 141957-94-0P 141957-95-1P 141957-96-2P 141957-97-3P 141957-98-4P 141957-99-5P 141958-00-1P** 141958-03-4P 141958-04-5P **142035-22-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(prepn. and neurokinin NK1 receptor antagonistic activity of (Erratum))
IT **134731-58-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and neurokinin NK1 receptor antagonistic activity of (Erratum))
IT **141958-01-2P 141958-02-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

(Reactant or reagent)
(prepn. and redn. of (Erratum))

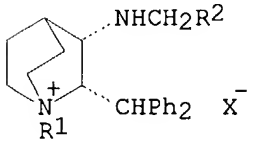
IT **142035-24-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of (Erratum))

L7 ANSWER 40 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:651241 CAPLUS
DOCUMENT NUMBER: 117:251241
TITLE: Preparation of N-alkylquinuclidinium salts as substance P antagonists
INVENTOR(S): Lowe, John A., III
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9212151	A1	19920723	WO 1991-US8836	19911204
W: AU, CA, FI, HU, JP, KR, NO, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE				
CA 2100163	AA	19920711	CA 1991-2100163	19911204
AU 9190947	A1	19920817	AU 1991-90947	19911204
AU 652407	B2	19940825		
EP 566589	A1	19931027	EP 1992-901108	19911204
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, SE				
JP 05508866	T2	19931209	JP 1992-501342	19911204
HU 65612	A2	19940728	HU 1993-1988	19911204
JP 07033385	B4	19950412	JP 1991-501342	19911204
ZA 9200148	A	19930709	ZA 1992-148	19920109
IL 100584	A1	19951031	IL 1992-100584	19921005
NO 9302513	A	19930709	NO 1993-2513	19930709

PRIORITY APPLN. INFO.: US 1991-639644 19910110
WO 1991-US8836 19911204

OTHER SOURCE(S): MARPAT 117:251241
GI



I

AB Title compds. [I; R1 = alkyl, allyl, phenylalkyl, carboxyalkyl, alkoxycarbonylalkyl; R2 = (substituted) Ph, thienyl, furyl, pyridyl; X = pharmaceutically acceptable counter ion], were prepd. as substance P antagonists (no data). Thus, (2S,3S)-cis-2-diphenylmethyl-N-[(2-methoxyphenyl)methyl]-1-azobicyclo[2.2.2]octan-3-amine was heated with MeI in EtOH to give 49% (2S,3S)-cis-I (R1 = Me, R2 = 2-MeOC6H4, X = iodo).

IT **144480-86-4P 144480-87-5P 144480-88-6P**
144480-91-1P 144480-93-3P 144480-94-4P
144480-95-5P 144480-96-6P

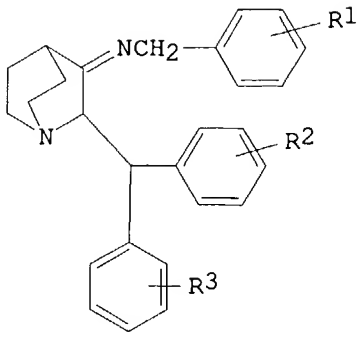
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of, as substance P antagonist)

L7 ANSWER 41 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:633862 CAPLUS
DOCUMENT NUMBER: 117:233862
TITLE: Preparation of 2-diphenylmethyl-N-phenylmethyl-1-azabicyclo[2.2.2]octan-3-imines and reduction products
INVENTOR(S): Godek, Dennis M.; Murtiashaw, Charles W.
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9212152	A1	19920723	WO 1991-US9186	19911218
W: AU, CA, DE, FI, HU, JP, KR, NO, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE				
US 5138060	A	19920811	US 1991-637102	19910103
AU 9191298	A1	19920817	AU 1991-91298	19911218
AU 653380	B2	19940929		
EP 565558	A1	19931020	EP 1992-901603	19911218
EP 565558	B1	19941214		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 05508867	T2	19931209	JP 1992-502391	19911218
ES 2065161	T3	19950201	ES 1992-901603	19911218
JP 07068244	B4	19950726	JP 1991-502391	19911218
CA 2098989	C	19980203	CA 1991-2098989	19911218
CA 2158130	C	19980714	CA 1991-2158130	19911218
ZA 9200008	A	19930702	ZA 1992-8	19920102
US 5216163	A	19930601	US 1992-861752	19920401
US 5442068	A	19950815	US 1993-3977	19930119
NO 9302431	A	19930702	NO 1993-2431	19930702
KR 9701157	B1	19970129	KR 1993-72007	19930702
JP 07316153	A2	19951205	JP 1994-322353	19941226
JP 2583026	B2	19970219		
JP 07316154	A2	19951205	JP 1994-322355	19941226
JP 2703193	B2	19980126		
JP 07330766	A2	19951219	JP 1994-322350	19941226
JP 2845425	B2	19990113		
FI 2000001108	A	20000510	FI 2000-1108	20000510
FI 2000001109	A	20000510	FI 2000-1109	20000510

PRIORITY APPLN. INFO.:
US 1991-637102 A1 19910103
CA 1991-2098989 A3 19911218
WO 1991-US9186 A 19911218
US 1992-861752 A3 19920401

OTHER SOURCE(S): CASREACT 117:233862; MARPAT 117:233862
GI



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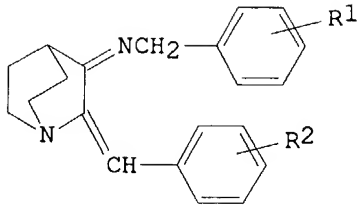


II

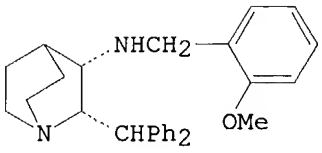
AB Title compds. (I; R1-R3 = H, F, Cl, Br, CF3, alkyl, alkoxy), were prepd. by reaction of exomethylene compd. II with R3C6H4A (A = MgCl, MgBr, Li). Thus, 2-phenylmethylene-1-azabicyclo[2.2.2]octan-3-one, 2-MeOC6H4CH2NH2, and camphorsulfonic acid were refluxed in PhMe with removal of H2O to give a soln. of the corresponding imine, which was added to a soln. of PhMgBr in THF at 5.degree. followed by stirring to room temp. over 12-18 h to give 30.5% I (R1 = 2-MeO, R2 = R3 = H). The latter compd. was reduced to the amine with Na(AcO)3BH (86.1%) followed by resoln. with mandelic acid to give a compd. said to be a substance P antagonist (intermediate).

IT **144408-24-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and decompn. of)

IT **134731-58-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and resoln. of)

IT **132746-60-2P 142035-24-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

L7 ANSWER 42 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:448289 CAPLUS
DOCUMENT NUMBER: 117:48289
TITLE: The discovery of (2S,3S)-cis-2-(diphenylmethyl)-N-[(2-methoxyphenyl)methyl]-1-azabicyclo[2.2.2]octan-3-amine as a novel, nonpeptide substance P antagonist
AUTHOR(S): Lowe, John A., III; Drozda, Susan E.; Snider, R. Michael; Longo, Kelly P.; Zorn, Stevin H.; Morrone, Jean; Jackson, Elisa R.; McLean, Stafford; Bryce, Dianne K.; et al.
CORPORATE SOURCE: Cent. Res. Div., Pfizer, Inc., Groton, CT, 06340, USA
SOURCE: Journal of Medicinal Chemistry (1992), 35(14), 2591-600
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB The structure-activity relationship of a series of quinuclidines is described which culminated in the first potent, selective, nonpeptide substance P (SP) antagonist, (2S,3S)-cis-2-(diphenylmethyl)-N-[(2-methoxyphenyl)methyl]-1-azabicyclo[2.2.2]octan-3-amine, (I; CP-96,345). I is a potent displacer of [3H]SP binding in human IM-9 cells and blocks SP-induced and capsaicin-induced plasma extravasation, as well as SP-induced salivation in the rat in vivo. I may both help to further the understanding of the interactions of small mols. with peptide receptors and serve to evaluate the therapeutic potential of a SP antagonist.

IT **141957-92-8P**
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and crystal structure of)

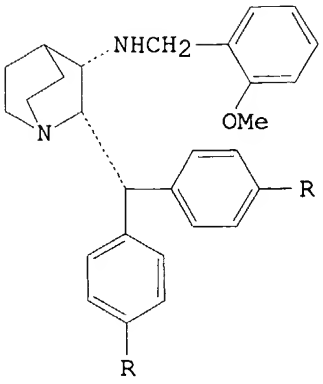
IT **135007-73-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and debenzylation of)

IT **132746-60-2P 134731-58-1P 135007-72-6P**
141957-93-9P 141957-94-0P 141957-95-1P
141957-96-2P 141957-97-3P 141957-98-4P
141957-99-5P 141958-00-1P 141958-03-4P 141958-04-5P
141958-05-6P **142035-22-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and neurokinin NK1 receptor antagonistic activity of)

IT **141958-01-2P 141958-02-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and redn. of)

IT **142035-24-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of)

L7 ANSWER 43 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:471348 CAPLUS
DOCUMENT NUMBER: 115:71348
TITLE: Preparation and radiolabeling of CP-96,345, the first non-peptide substance P antagonist
AUTHOR(S): Lowe, John A., III; Drozda, Susan E.; Snider, R. Michael; Longo, Kelly P.; Bordner, Jon
CORPORATE SOURCE: Cent. Res. Div., Pfizer, Inc., Groton, CT, 06340, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (1991), 1(2), 129-32
CODEN: BMCLE8; ISSN: 0960-894X
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB The prepn. of CP-96,345 I (R = H), a potent, non-peptide Substance P antagonist, in both enantiomerically pure and radiolabeled form I (R = 3H) is described. In addn., the abs. configuration of (-)-I (R = H) was detd. to be 2S,3S.

IT **134731-58-1P 135007-71-5P 135007-72-6P 135007-77-1P 135095-42-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and substance P antagonist activity of)

IT **135007-76-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and tritiation of)

IT **135007-73-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and N-debenzylation of, with hydrobromic acid)

IT **132746-60-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn., abs. configuration, and substance P antagonist activity of)

L7 ANSWER 44 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:81592 CAPLUS
DOCUMENT NUMBER: 114:81592
TITLE: Preparation of 3-amino-2-benzylquinuclidines as substance P antagonists
INVENTOR(S): Lowe, John A., III
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9005525	A1	19900531	WO 1988-US4205	19881123
W: FI, HU, NO, RO, SU, US				
WO 9005729	A1	19900531	WO 1989-US5338	19891120
W: AU, BB, BG, FI, HU, JP, KR, LK, MC, MG, MW, NO, RO, SD, SU, US				
RW: AT, BE, BF, BJ, CF, CG, CH, CM, DE, ES, FR, GA, GB, IT, LU, ML, MR, NL, SE, SN, TD, TG				
AU 8946619	A1	19900612	AU 1989-46619	19891120
AU 617906	B2	19911205		

EP 409931	A1	19910130	EP 1990-901247	19891120
EP 409931	B1	19940216		
R: AT, BE, CH, DE, ES, FR, GB, IT, LI, LU, NL, SE				
JP 03503768	T2	19910822	JP 1990-501319	19891120
RO 106743	B1	19930630	RO 1989-145605	19891120
AT 101608	E	19940315	AT 1990-901247	19891120
JP 06047589	B4	19940622	JP 1989-501319	19891120
ES 2062504	T3	19941216	ES 1990-901247	19891120
CA 2003441	AA	19900523	CA 1989-2003441	19891121
CA 2003441	C	19980407		
CN 1043130	A	19900620	CN 1989-109556	19891122
CN 1026111	B	19941005		
ZA 8908901	A	19911030	ZA 1989-8901	19891122
DD 285605	A5	19901219	DD 1989-334812	19891123
PL 161864	B1	19930831	PL 1989-282431	19891123
NO 9003254	A	19900920	NO 1990-3254	19900720
NO 174584	B	19940221		
NO 174584	C	19940601		
US 5162339	A	19921110	US 1990-566338	19900720

PRIORITY APPLN. INFO.: WO 1988-US4205 A2 19881123
EP 1990-901247 A 19891120
WO 1989-US5338 A 19891120

OTHER SOURCE(S): MARPAT 114:81592

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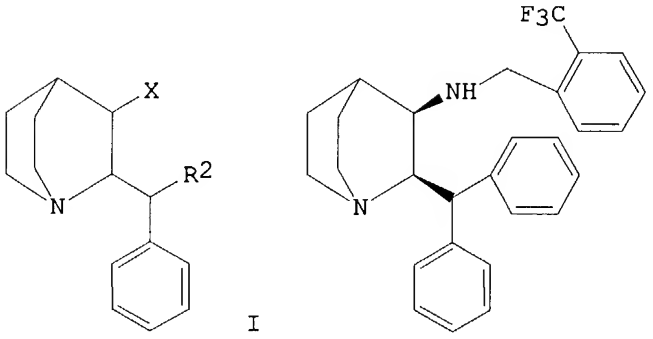

I II

AB The title compds. [I; X = NHCH2R1, :NCH2R1, N:CHR1; R1 = cycloalkyl, norbornyl, pyrrolyl, thienyl, pyridyl, indolyl, biphenyl, (substituted) Ph; R2 = branched alkyl, alkenyl, cycloalkyl, furyl, thienyl, pyridyl, indolyl, biphenyl, (substituted) Ph], were prepd. Thus, 3-keto-2-benzhydrylquinuclidine and 2-F3CC6H4CH2NH2 in PhMe contg. comphorsulfonic acid were refluxed through a Dean-Stark trap to give the imine, which was reduced to give title compd. II. II at 32 mg/kg orally in rats showed 50% inhibition in the rat foot edema test.

IT 53898-72-9P 129912-86-3P 129912-87-4P 129912-88-5P
129912-89-6P 129912-90-9P 129912-91-0P
129912-92-1P 129912-93-2P 129912-94-3P 129912-95-4P
135007-71-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as intermediate for substance P antagonists)

IT 129912-31-8P **129912-33-0P 129912-35-2P** 129912-37-4P
129912-38-5P 129912-39-6P 129912-40-9P 129912-41-0P
129912-44-3P 129912-46-5P 129912-47-6P
129912-48-7P 129912-49-8P 129912-50-1P

129912-51-2P 129912-52-3P 129912-53-4P
129912-54-5P 129912-55-6P 129912-56-7P
129912-57-8P 129912-58-9P 129912-59-0P
129912-60-3P 129912-61-4P 129912-62-5P
129912-63-6P 129912-64-7P 129912-65-8P **129912-66-9P**
129912-67-0P 129912-68-1P 129912-69-2P
129912-70-5P 129912-71-6P 129912-72-7P 129912-73-8P
129912-74-9P 129912-75-0P 129912-76-1P 129912-77-2P
129912-78-3P 129912-79-4P 129912-80-7P
129912-81-8P 129912-82-9P **129912-83-0P**
129912-84-1P 129912-85-2P 131787-13-8P
134731-58-1P 135007-72-6P 141957-93-9P
141957-94-0P 141957-95-1P 141957-96-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as substance P antagonists)

L7 ANSWER 45 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1975:508143 CAPLUS
DOCUMENT NUMBER: 83:108143
TITLE: Quinuclidine chemistry. 4. Diuretic properties of cis-3-amino-2-benzhydrylquinuclidine
AUTHOR(S): Warawa, E. J.; Mueller, N. J.; Fleming, J. Stuart
CORPORATE SOURCE: Res. Lab., Aldrich Chem. Co., Inc., Milwaukee, WI, USA
SOURCE: Journal of Medicinal Chemistry (1975), 18(6), 587-93
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 83:108143
GI For diagram(s), see printed CA Issue.
AB 2-Benzhydryl-3-quinuclidinone [32531-66-1] was condensed with benzylamine [100-46-9], followed by redn., chromatog. sepn. of isomers, and debenzylation to give cis-3-amino-2-benzhydrylquinuclidine (I) [32531-19-4], the most active of 15 title compds. prepd. and tested in rats and dogs for urine prodn. and K and Na excretion. I was more active than its trans isomer [32531-24-1] and hydroflumethiazide [135-09-1] but less active than furosemide [54-31-9]. Structure-activity relations and renal site of action of the compds. is discussed.
IT 32531-19-4P 32531-21-8P 32531-24-1P **32531-25-2P**
32531-26-3P 32531-28-5P 32531-33-2P 56326-62-6P 56326-63-7P
56326-64-8P 56326-65-9P 56326-68-2P 56326-73-9P **135007-71-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and diuretic activity of)
IT **32531-18-3P** 32531-20-7P 56326-70-6P 56326-71-7P
56326-74-0P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

L7 ANSWER 46 OF 46 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1971:405735 CAPLUS
DOCUMENT NUMBER: 75:5735
TITLE: 2-Benzhydrylquinuclidines as diuretics
INVENTOR(S): Warawa, Edward J.
PATENT ASSIGNEE(S): Aldrich Chemical Co., Inc.
SOURCE: U.S., 12 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3560510	A	19710202	US 1969-804691	19690305

PRIORITY APPLN. INFO.: US 1969-804691 19690305

GI For diagram(s), see printed CA Issue.

AB Cis and trans isomers of the title compds. are obtained by isolating the cis or trans isomer from a mixt. of cis,trans-2-benzhydryl-3-(benzylamino)quinuclidines by chromatog. and subsequent catalytic debenzylation. Alternatively, a mixt. of cis,trans-3-amino analog is acetylated with Ac2O and the 3-acetamido derivs. sepd. by fractional crystn. from iso-PrOH and hydrolyzed in concd. HCl. BzH reacted with 3-quinuclidinone in alc. in the presence of a base, the 2-benzylidene-3-quinuclidinone treated with PhMgBr in Et2O-C6H6, the resultant 2-benzhydryl-3-quinuclidinone distd. azeotropically with PhCH2NH2 in PhMe in the presence of p-MeC6H4SO3H, and the 2-benzhydryl-3-(benzylimino)quinuclidine reduced with NaBH4 yielded pure cis-I.

IT 24782-61-4P 24782-62-5P 24802-69-5P 24802-70-8P **32531-18-3P**
32531-19-4P 32531-20-7P 32531-21-8P 32531-22-9P 32531-23-0P
32531-24-1P **32531-25-2P** 32531-26-3P 32531-27-4P
32531-28-5P 32531-29-6P 32531-30-9P 32531-31-0P 32531-32-1P
32531-33-2P 32531-34-3P 32531-66-1P 32531-67-2P 32531-68-3P
135007-71-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)